For Reference

NOT TO BE TAKEN FROM THIS ROOM

For Reference

NOT TO BE TAKEN FROM THIS ROOM

Ex LIBRIS
UNIVERSITATIS
ALBERTAENSIS

UNIVERSITY OF ALBERTA
QUAECUMQUE VERA

University of Alberta

Digitized by the Internet Archive
in 2019 with funding from
University of Alberta Libraries

https://archive.org/details/Cooke1964

Thesis
1965
H 25

THE UNIVERSITY OF ALBERTA

AN APPROACH TO THE SYNTHESIS OF LYCOPODIUM ALKALOIDS

by

GEORGE ALEXANDER COOKE, M.Sc.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

DECEMBER 11, 1964.

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "An Approach to the Synthesis of Lycopodium Alkaloids," submitted by George Alexander Cooke, M.Sc., in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

ACKNOWLEDGEMENTS

The author wishes to thank:

Dr. W. A. Ayer for untiring patience, assistance, and optimism through the entire course of this project.

The University of Alberta and the National Research Council for financial support.

Mrs. Glen Johnston for typing this thesis.

My wife Elaine, without whose encouragement this work would not have been undertaken, and could not have been completed.

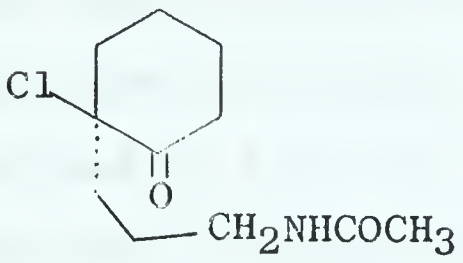
This thesis is dedicated to the memory

of my son

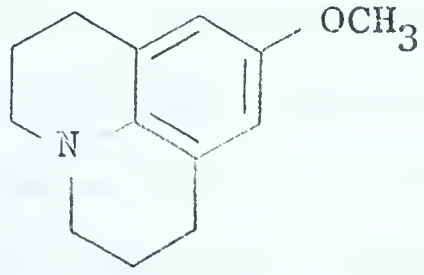
Julian MacDonald Cooke

ABSTRACT

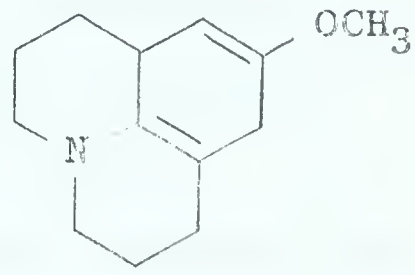
The compound N-acetyl-2-chloro-2-(3-aminopropyl)-cyclohexanone (LXXXI) has been prepared by the alkylation of the pyrrolidine enamine of cyclohexanone, followed by hydride reduction of the corresponding ethylene ketal, acetylation, hydrolysis of the ketal, and chlorination of the resulting N-acetyl ketone.



LXXXI

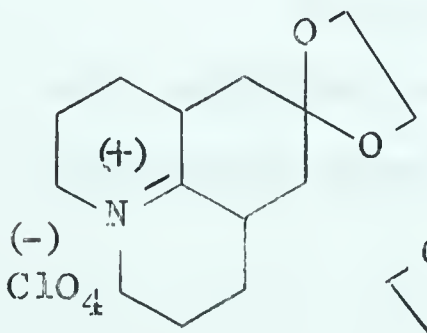


XXVIII

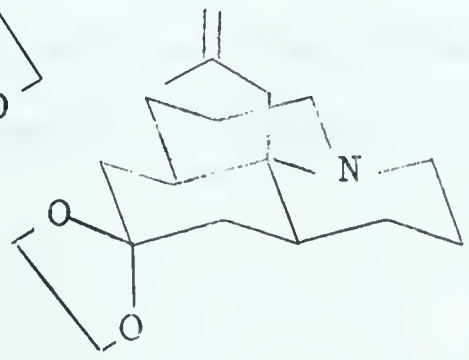


XXXVI

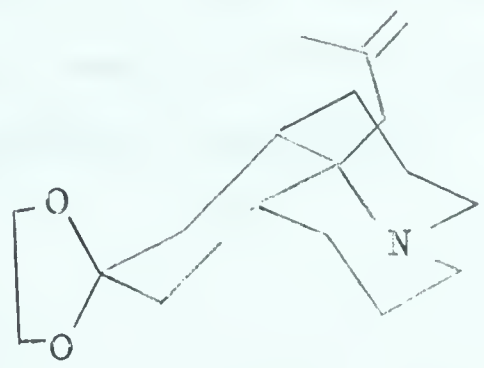
In a more direct approach to a lycopodine system, a series of hexahydrojulolidine derivatives, oxygenated at C-9 and carrying a substituent at C-11, were prepared. Thus Birch reduction of 9-methoxyjulolidine XXVIII yielded the dihydro-derivative XXXVI which on treatment with ethylene glycol and perchloric acid was converted to the ethylene-ketal iminium perchlorate XCVIII. This



XCVIII

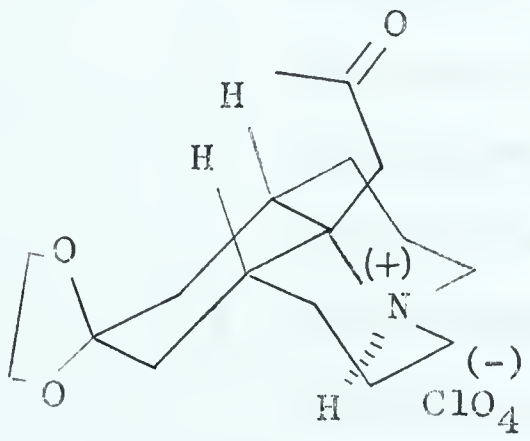


CX

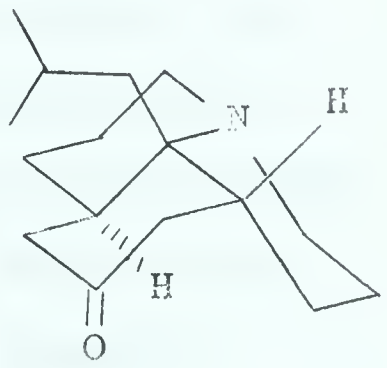


CXI

substance was then subjected to the conditions of the Grignard reaction using methallyl magnesium chloride (CVII) to produce the corresponding C-11 adduct as two stereoisomers CX (all trans) and CXI (all cis), the latter being the major product. Pure CXI was obtained by column chromatography and experiments were carried out to determine its stereochemistry. Treatment of the CXI (as its perchlorate) with ozone followed by catalytic reduction of the ozonide produced the ketone CXXIII and several attempts were made to convert this to the annotinine II skeleton by photochemical methods. Reactions were as well performed designed to introduce unsaturation at C-7a, 8 thus providing a compound which might be expected to produce the cis-trans isomer (CXLIV) on dissolving metal reduction.



CXXIII



CXLIV

The mass spectra of several of these derivatives were measured and are interpreted by analogy with fragmentations observed in several Lycopodium alkaloids.

CONTENTS

	PAGE
1. Introduction	1
2. Discussion	20
A. The Cyclohexanone-Type Model Series	20
1. The Formation of the 2-Keto-propyl Group	21
2. The Formation of the 3-Amino-propyl Group	27
3. Attempts to Prepare the 2-Cyclo-hexen-1-one LXXII	30
4. The Formation of N-Haloamides	35
B. The Julolidine Series	39
1. The Preparation of XXVIII and Related Phenols	41
2. The Birch Reduction of XXVIII and the Formation of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine XCIX	46
3. The Grignard Reaction Using Allyl Bromide and Methallyl Chloride	58
4. Stereochemistry	68
5. The Preparation of 9-Ethylenedioxy-11-(2-ketopropyl)-7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate CXXIII and Attempts at its Photochemical Conversion	77

PAGE

6. Reactions Involving the Olefinic Linkage of 9-Ethylenedioxy-11-methallyl hexahydrojulolidine CVIII other than Conversion to CXXIII 90

7. The Introduction of Unsaturation at Carbon 7a 98

8. The Mass Spectra of Representative Hexahydrojulolidine Derivatives 105

3. Experimental 117

4. Figures 159

(a) Infrared Spectra 159

(b) Nuclear Magnetic Resonance Spectra 164

(c) Mass Spectra 168

5. References 174

FIGURES

Page

(a) Infrared Spectra

1. N-acetyl-2-(3-aminopropyl)cyclohexanone 2,4-dinitrophenylhydrazone LXXX 159
2. 9-Methoxy-8,10-dihydrojulolidine perchlorate XXXVI 159
3. 9-Ethylenedioxy-8,9,10,11-tetrahydro-julolidine perchlorate XCVIII 160
4. 9-Ethylenedioxy-11-allyl-7a,8,9,10,10a,11-hexahydrojulolidine CV 160
5. 11-(2-Ketopropyl)-7a,8,9,10,10a,11-hexahydrojulolidine perchlorate CXXII 161
6. 9-Ethylenedioxy-11-(2-ketopropyl)-7a,8,9,10,10a,11-hexahydrojulolidine perchlorate CXXII 161
7. The rearranged ketone CXXXV 162
8. 9-Ethylenedioxy-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine CXLV 162
9. 9-Keto-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine CXLVI 163
10. 8-Bromo-9-keto-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine CXLVII 163

(b) Nuclear Magnetic Resonance Spectra

11. 9-Methoxyjulolidine XXVIII 164
12. 9-Hydroxyjulolidine perchlorate 164

Page

13. 9-Ethylenedioxy-9,10,10a,11-tetrahydrojulolidine XCIX 165

14. 9-Ethylenedioxy-11-allyl-7a,8,9,10,10a,11-hexahydrojulolidine CV 165

15. 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CVIII (carbon tetrachloride) 166

16. 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CVIII (benzene) 166

17. Cis-cis-9-ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CXI (benzene) 167

18. The rearranged ketone CXXXV 167

(c) Mass Spectra

19. 6-Methoxy-1,2,3,4-tetrahydroquinoline XCIII 168

20. 9-Methoxyjulolidine XXVIII 168

21. 9-Hydroxyjulolidine XCV 169

22. 9-Keto-7a,8,9,10,10a,11-hexahydrojulolidine ethylene thioketal CLI 170

23. 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CVIII 171

24. 9-Methoxy-7a,8,10a,11-tetrahydrojulolidine XCVI 171

25. 9-Keto-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine CXLVI 172

Page

26. 9-Ethylenedioxy-11-isobutyl-7a,8,9,10, 10a,11-hexahydrojulolidine CXLV 172

27. The rearranged ketone CXXXV 173

28. 9-Ethylenedioxy-11-allyl-7a,8,9,10,10a,11-hexahydrojulolidine CV 173

TABLES

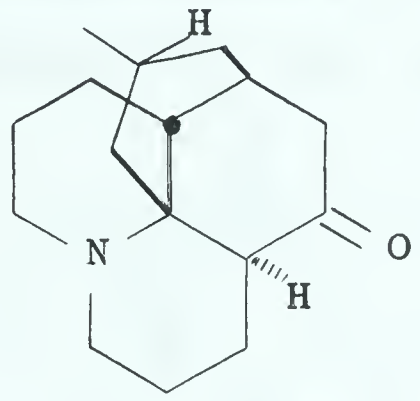
Page

1. The NMR Spectrum of Thalline XCIII in Carbon Tetrachloride 42
2. The Birch Reduction of 9-Methoxyjulolidine XXVIII 49
3. Chromatography of the Products of Michael Addition 118
4. Column Chromatography of CVIII 145

INTRODUCTION

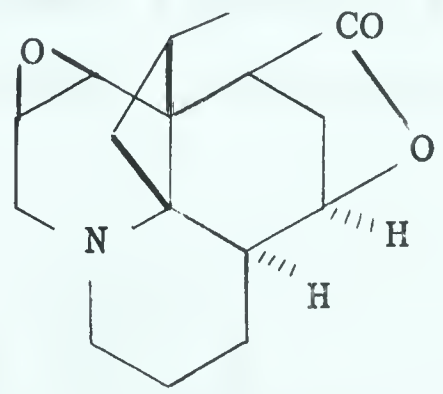
The development in recent years of structural proposals for a number of the lycopodium alkaloids has stimulated interest in synthetic approaches to these substances both as a problem of intrinsic interest, and also as the final step in a classical structural analysis.

The structure of lycopodine I itself was proposed by MacLean (1) after an intensive study by several



I

groups. The relative and absolute configuration of I was first suggested by Anet (2) in 1960, and is shown by structure I. Earlier, annotinine had been shown to have structure II (3) which has been confirmed by X-ray

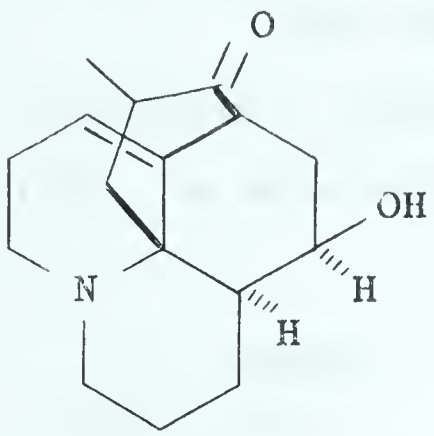


II

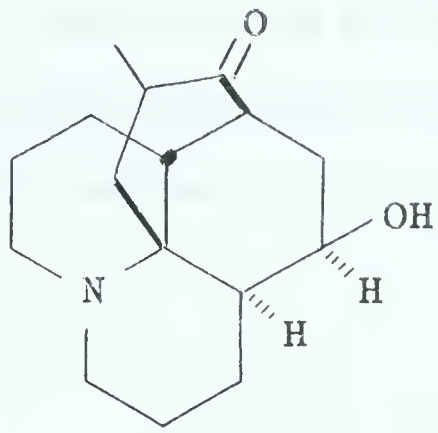
crystallography (4, 5). This later study (5) also showed clearly the relative stereochemistry of annotinine II. The

absolute stereochemistry of annotinine and lycopodine, as shown by II and I respectively, was determined by Wiesner, Valenta, and co-workers (6) in 1961 and in the case of I has been confirmed by an application of the axial halo-ketone rule (7).

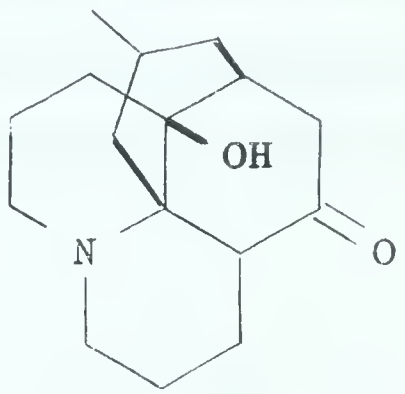
Following the determination of the structure of lycopodine I in 1960, the structures of several other lycopodium alkaloids were rapidly elucidated. Many of these, such as acrifoline III (8), annofoline IV (9), and



III

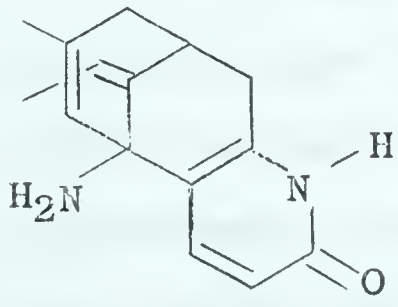


IV

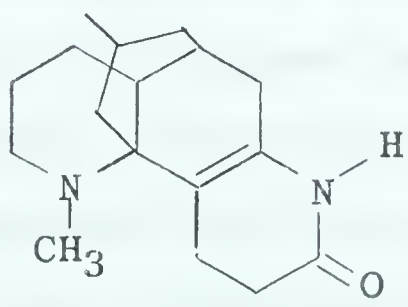


V

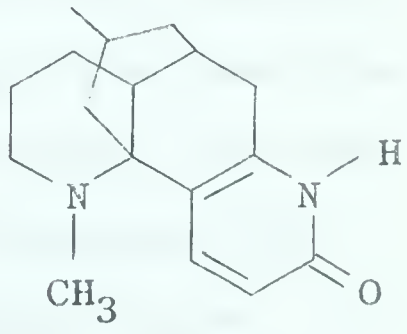
lycodoline V (10) have the lycopodine skeleton. However, a group of dinitrogenous lycopodium alkaloids were shown to differ from this pattern. This group included selagine VI



VI

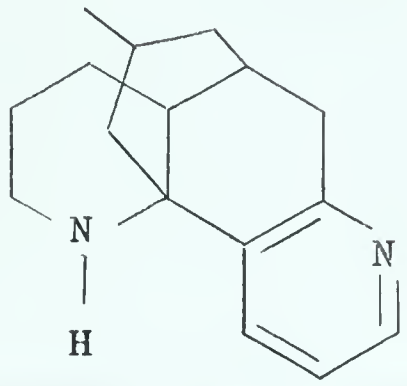


VII



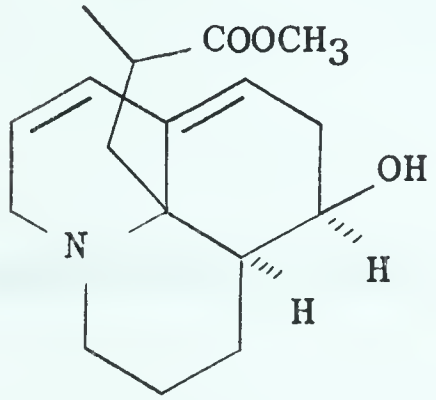
VIII

(11) α-obscurine VII and β-obscurine VIII (12) and lycodine IX (13).

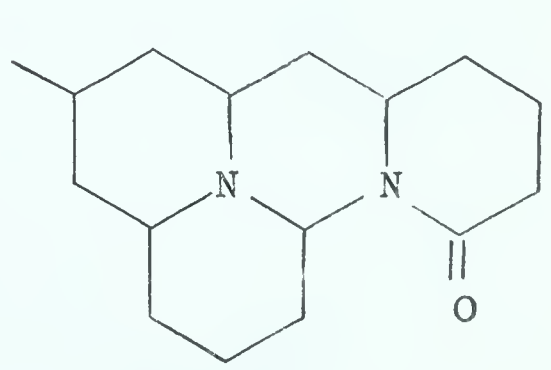


IX

This year, several new structural types have been elucidated. Lyconnotine has been shown to have structure X (14). A more radical change from the lycopodine skeleton



X

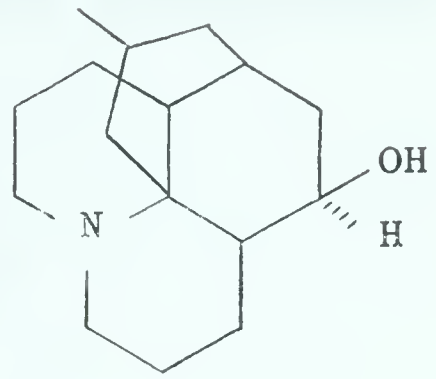


XI

has been suggested (15) for cernuine XI.

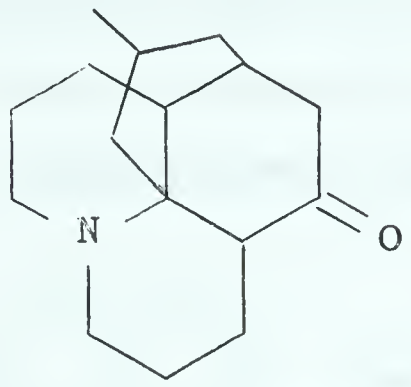
Synthetic studies in the field of the lycopodium alkaloids have thus far centered mainly on transformations within various groups. Thus Ayer and co-workers (12) have transformed α-obscurine VII into dihydrolycopodine XII. Anet and Rao (16) have transformed lycopodine I into

VII

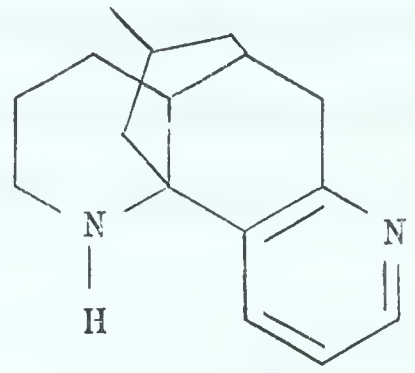


XII

lycodine IX, and Ayer, Law, and Piers (17) have prepared



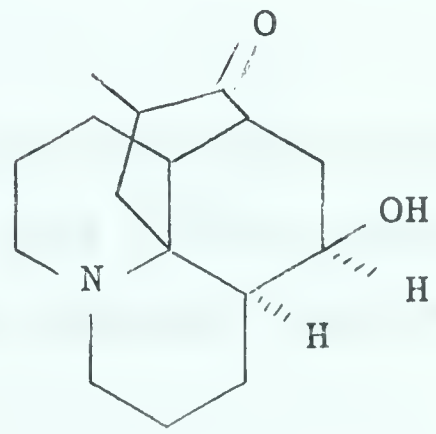
I



IX

annofoline IV from lycopodine I.

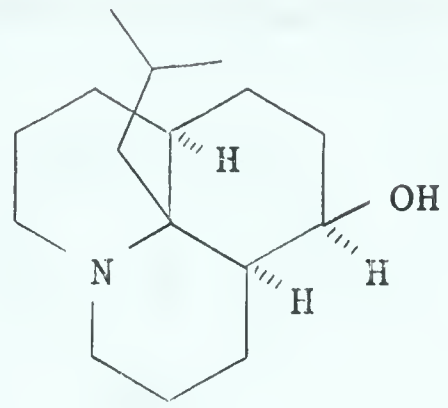
I



IV

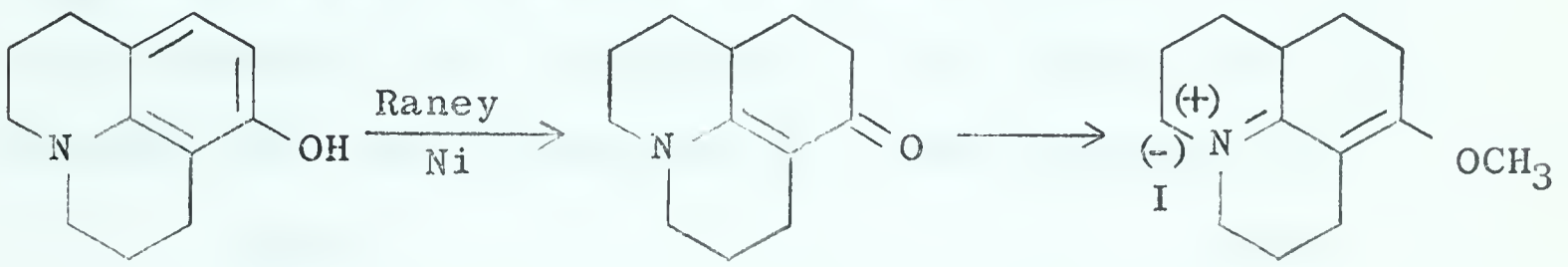
Very recently Valenta, Wiesner and co-workers (18) have confirmed the structure of lyconnotine X by a total synthesis of the racemic alcohol XIII, which is a trans-

formation product of X. Their synthesis involved Raney



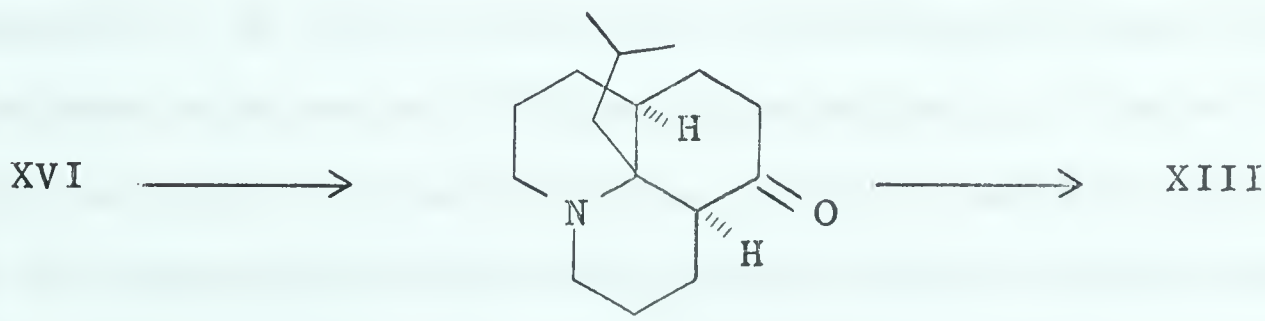
XIII

nickel reduction of the phenol XIV to form the α,β-unsaturated ketone XV which on treatment with boiling methyl iodide afforded the iminium iodide XVI. Reaction of XVI



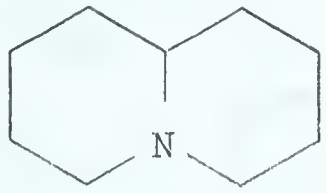
XIV XV XVI

with isobutyl lithium followed by acid hydrolysis yielded the ketone XVII, which on reduction with lithium aluminium hydride gave the alcohol XIII. This synthesis represents



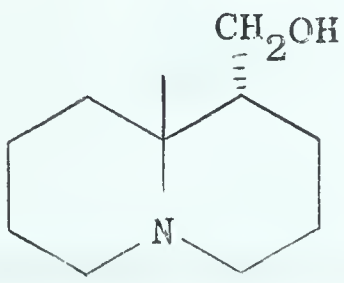
XVII

the first entry into the lycopodine ring system beginning with "readily available starting materials."

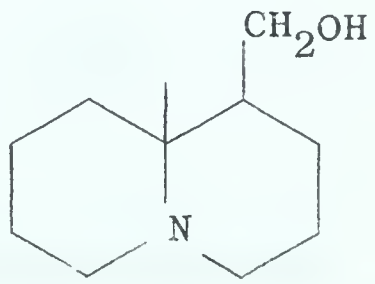


XVIII

In considering methods of approach to I, it was noted that I is a derivative of quinolizidine XVIII and so thought was given to utilizing a type of synthesis of a bridge system containing rings A, B and D of I based on biogenetic models. This plan had been used with success by Van Tamelen (19) in syntheses of the lupine alkaloids lupinine XIX and epilupinine XX. These compounds are

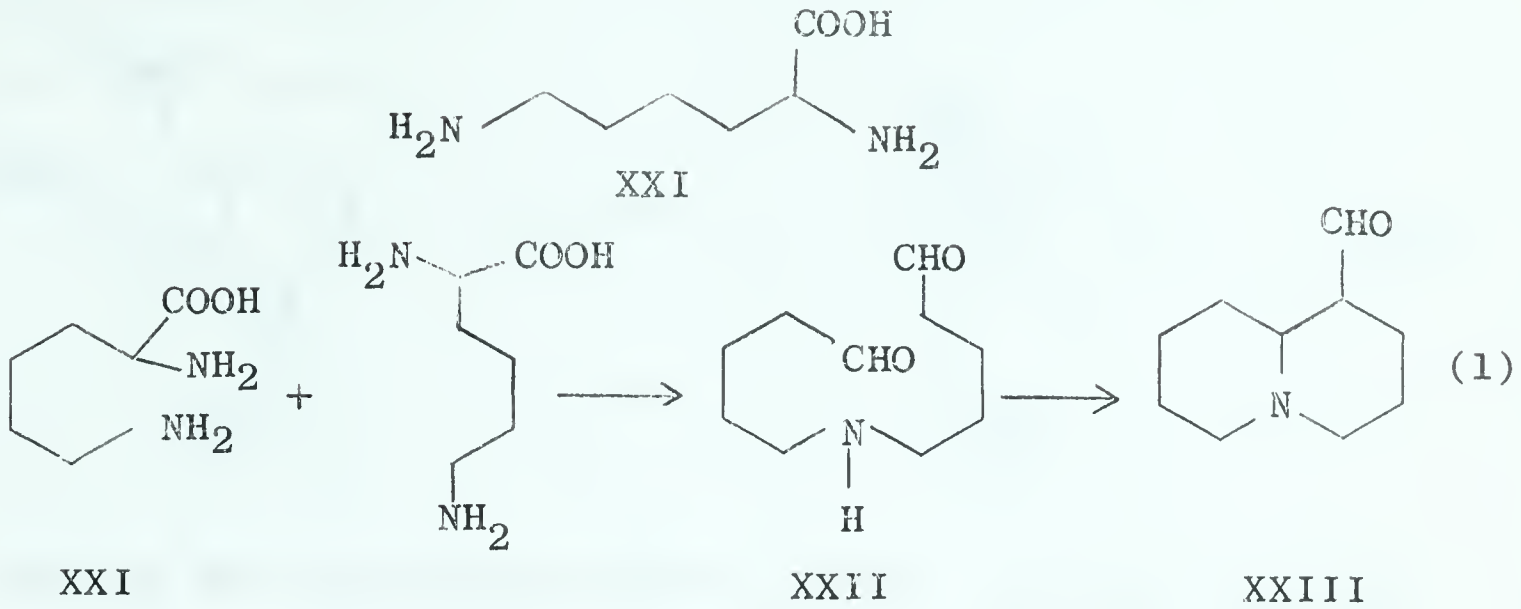


XIX

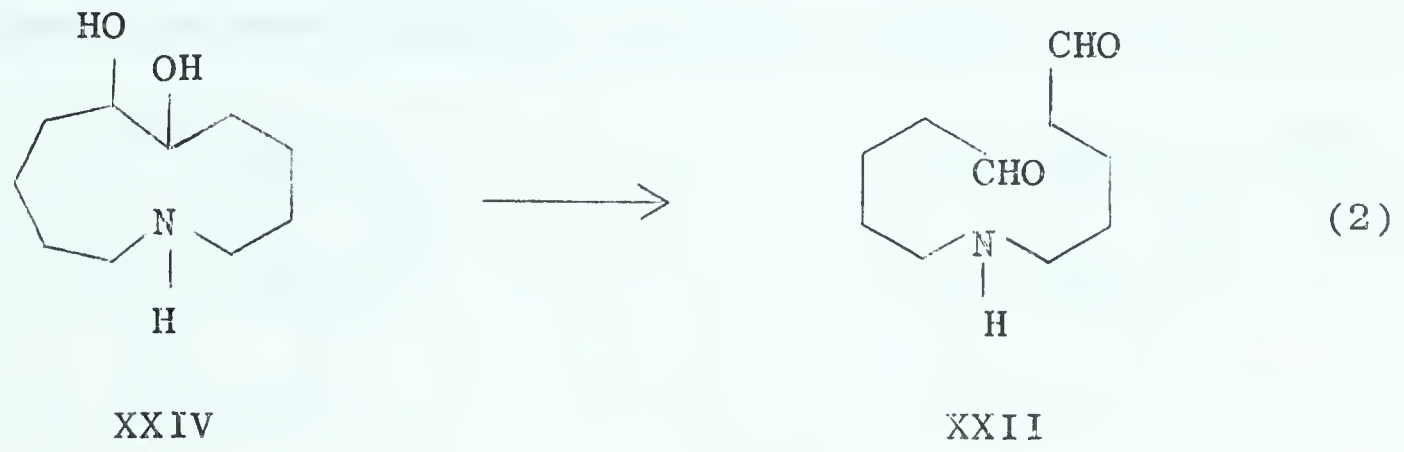


XX

thought to be derived from the diamino-acid lysine XXI by a scheme such as is outlined in equation 1. The critical step in such a sequence is the internal Mannich reaction of the amino-dialdehyde XXII to the quinolizidine XXIII. When Van Tamelen (19) carried out this reaction using XXII derived from the eleven-membered cycle XXIV by



periodate cleavage (equation 2), the derivative XXIII was produced, which on reduction with lithium aluminum hydride



produced material identical with DL-epilupinine XX.

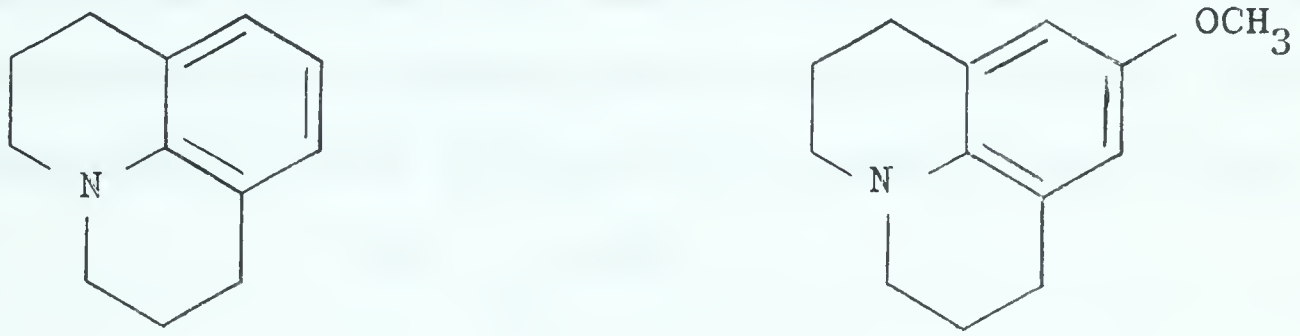
Such a scheme seemed readily adaptable to our needs. If an amino-diketone such as XXV could be prepared, it might be expected to undergo an internal Mannich reaction to produce the tricyclic amino-ketone XXVI, as in equation 3, in obvious analogy with the sequence in equation 1. The first part of the work to be reported in this thesis therefore deals with attempts to prepare a compound suitable for this type of reaction.

Another line of approach to the key area of formation of the bridge-ring of I which was considered was



XXV XXVI (3)

through the julolidine (XXVII) series. In this compound, or in the one actually used, 9-methoxyjulolidine (XXVIII), three of the four rings of I were already present. The bridge-ring when in place would be attached to carbons which

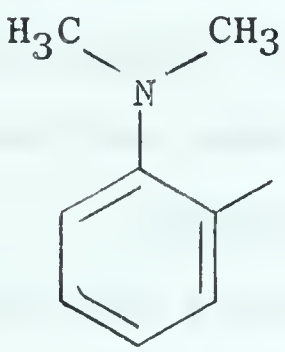


XXVII XXVIII

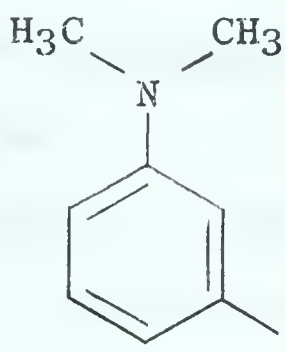
are now ortho and para to the methoxyl group of XXVIII. The system XXVIII of course would have to be extensively modified before this could take place. The primary modification will be the creation of a reactive centre at C-11 through, in our opinion, a Birch reduction of the substituted aniline XXVIII.

Compound XXVIII is essentially an N,N-dialkyl-2,4,6-trisubstituted aniline. The Birch reduction of such highly substituted aromatic amines has not been well investigated. Birch (20) has investigated the reduction of

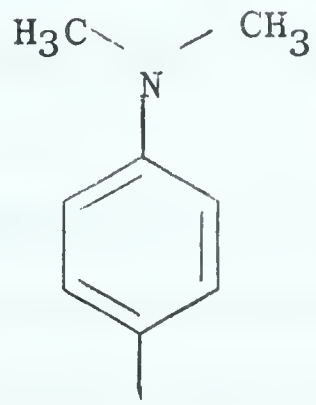
the somewhat analogous N,N-dimethyltoluidines XXIX, XXX, and XXXI by means of sodium and alcohol in liquid ammonia.



XXIX

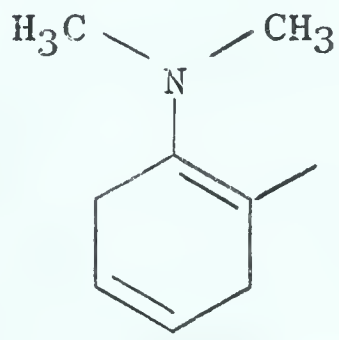


XXX



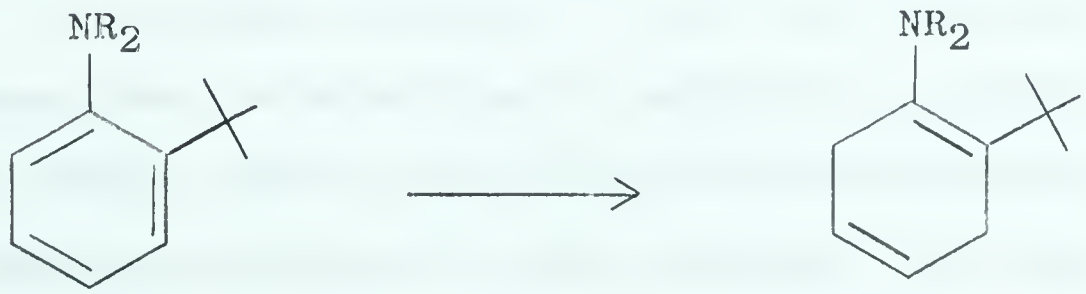
XXXI

In all three cases a dihydro reduction product containing an enamine was obtained, for example XXXII from XXIX. More recently Stork (21) investigated the reduction of 2-t-butyl-anilines (XXXIII) with sodium/alcohol/ammonia and lithium/



XXXII

t-butanol/ammonia. The reactions are summarized in equation 4. Use of the former reduction system gave



R = CH_3, H

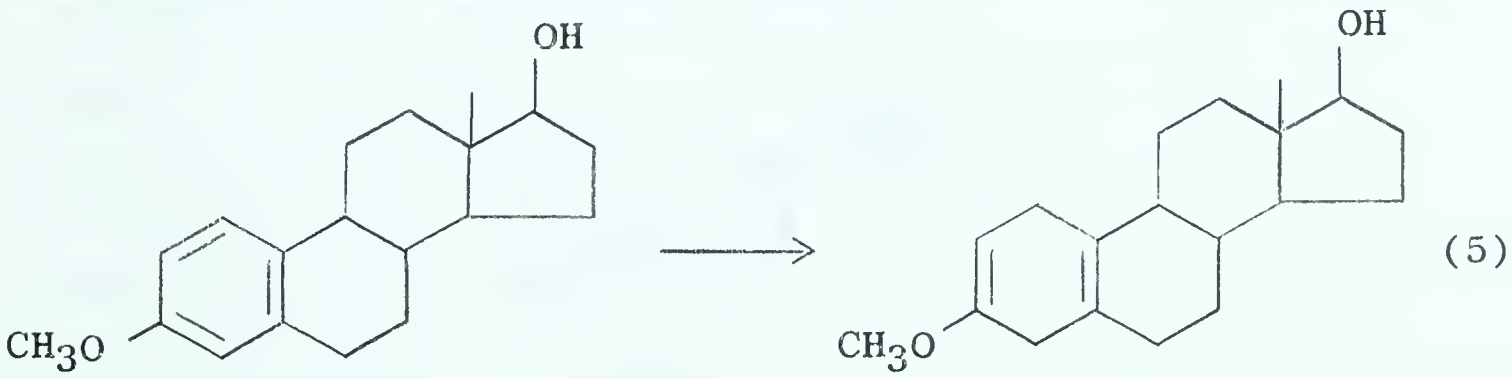
XXXIII

XXXIV

(4)

approximately 10% yields of XXXIV, whereas the latter afforded XXXIV in 50-70%. Stork states also that in the case of XXXIV (R=H), there was no evidence of tautomerism of the enamine to the corresponding imine under either set of reaction conditions.

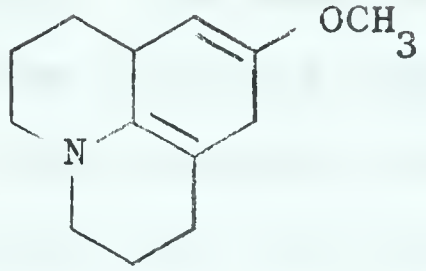
Compound XXVIII is also essentially a 3,4,5-trisubstituted anisole. The Birch reduction of substituted anisoles has been extensively investigated, particularly as a part of the synthesis of 19-nor steroids, and a large variety of conditions has been developed. For example, the reduction of estradiol 3-methyl ether XXXV was carried out using lithium/t-butanol/iron-free ammonia to the extent (22, 23) of greater than 99%. The reaction is summarized in equation 5.



(5)

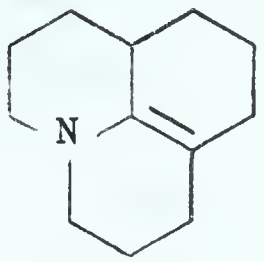
XXXV

For these reasons, it was felt that XXVIII would be susceptible to this type of reduction to produce an enamine XXXVI, whose lability would satisfactorily activate the unsaturated carbon α to the nitrogen. In view of the well known (21, 22) ease of hydrolysis of enamines, it should be noted that Leonard (24) has found the closely



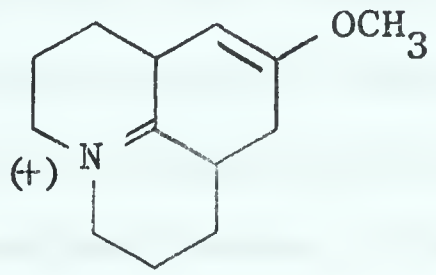
XXXVI

related enamine XXXVII to be hydrolytically stable.



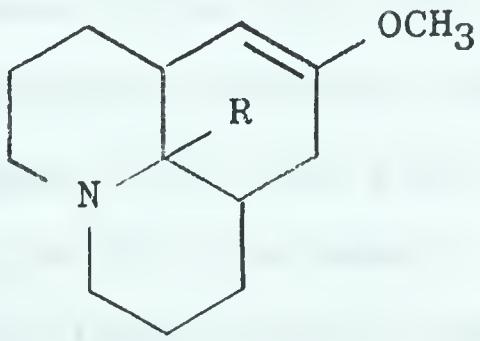
XXXVII

The reaction to be carried out on XXXVI was visualized to be a type of reductive alkylation of the tautomeric iminium compound XXXVIII to produce a system



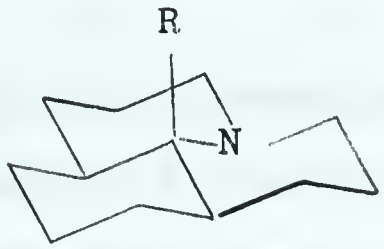
XXXVIII

in which the three ring junction carbon atoms are

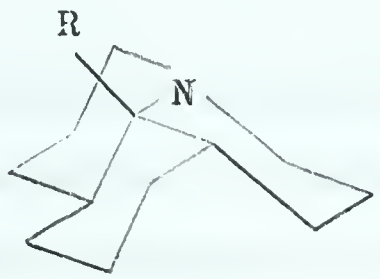


XXXIX

saturated, as in XXXIX. The question of possible configurational isomerism involving these centres is thus raised. There are three possible isomeric hexahydrojulolidines XL, XLI and XLII and there is no a priori



XL

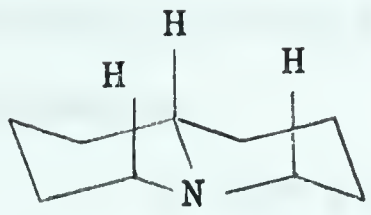


XLI

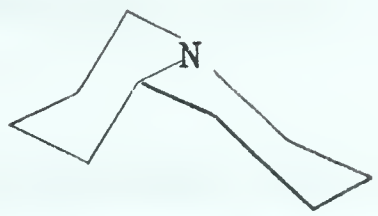


XLII

reason why any one or all of them could not form in an alkylation reaction such as is suggested above. Thus any aids in stereochemical identification would be welcome. Bohlmann (25) in work on quinolizidine systems, has found that in these compounds, the presence of at least two carbon-hydrogen bonds oriented trans-diaxially to the unshared pair on the nitrogen results in the appearance of a series of well defined bands in the 2900-2600 cm^{-1} region of their infrared spectrum. These bands are termed "Bohlmann bands," an example of a compound giving rise to them being shown as XLIII, and one which doesn't as XLIV. Comparison of these latter two with structures XL, XLI, and XLII make it immediately apparent that XL and XLII will show Bohlmann bands, while XLI will not. Such has been found (25) to be in fact the case. In a more analogous situation Ayer and Iverach (10), investigating the structure

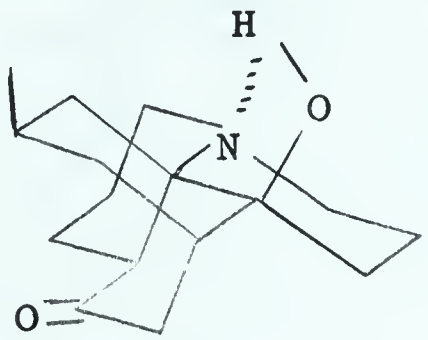


XLIII

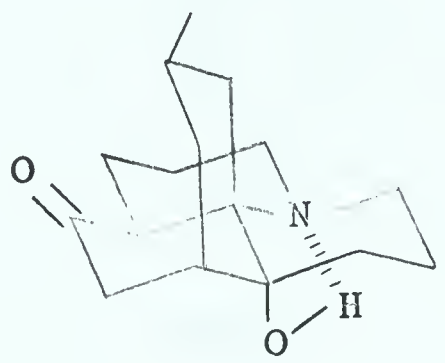


XLIV

of the lycopodium alkaloid lycodoline, were able on the basis of chemical evidence to reduce the structural possibilities for this compound to XLV and XLVI. Since

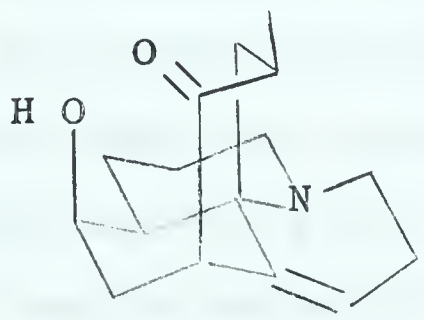


XLV



XLVI

the infrared spectrum of the authentic substance displayed no Bohlmann bands, structure XLV was accordingly assigned. A related alkaloid, acrifoline III, which has stereo-

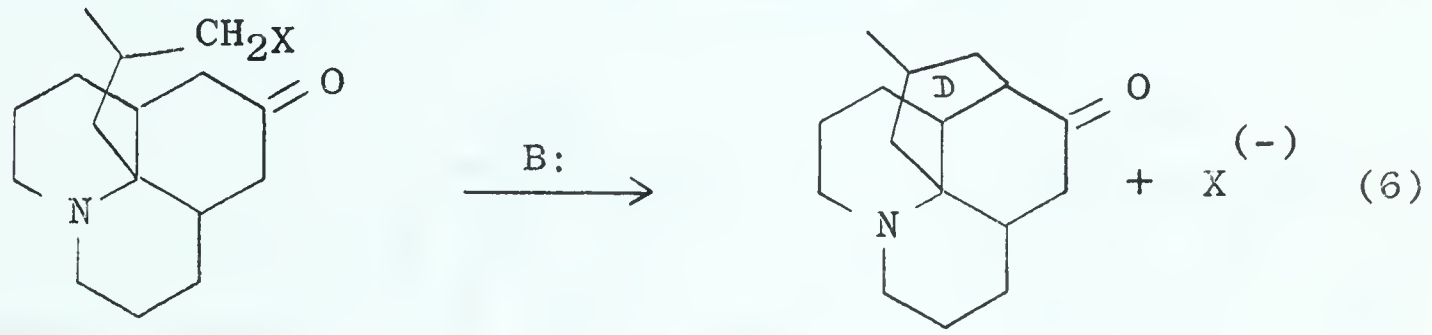


III

chemistry similar to XLVI, displays prominent Bohlmann bands. It was thus expected that the presence or absence

of this feature in the infrared spectra of our synthetic intermediates would be of considerable utility in structural assignments.

It was felt from the beginning that the development of a sequence leading to formation of ring D of I would be an aspect of the synthesis which would present some difficulty. The scheme as visualized involved a carbanionic reaction of the type indicated in equation 6. It will

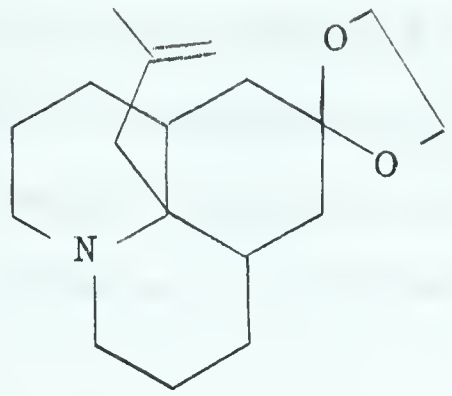


(6)

XLVII XLVIII

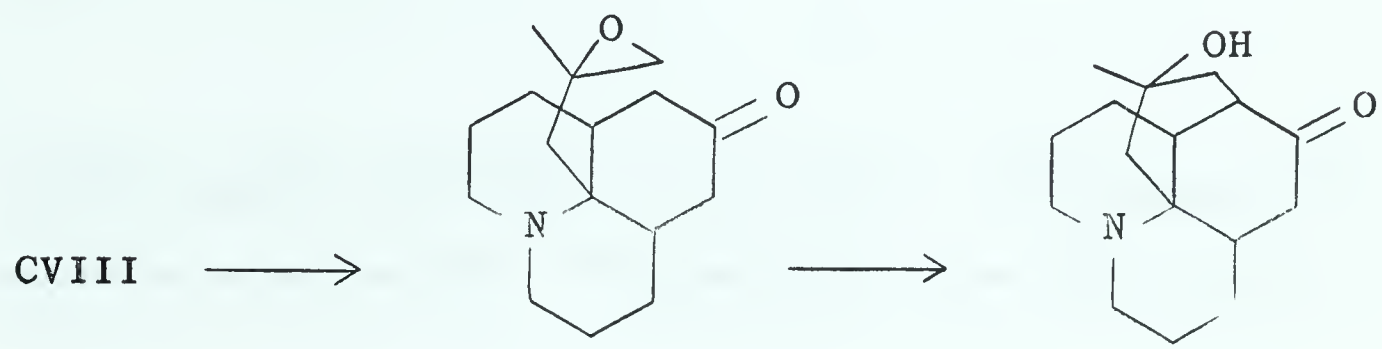
be recalled that the ring D methyl group of I is in the equatorial conformation. The reaction in equation 6 does not specifically contain provision for this feature, or the opportunity to bring it about after XLVIII has formed. The development of a method whereby the ring could be closed while at the same time preserving a reactive center in the bridge-ring was thus given some consideration. The compound at hand was the methallyl-ethyleneketal CVIII.

Perhaps the simplest way in which this could be accomplished would be via an epoxide, as indicated in



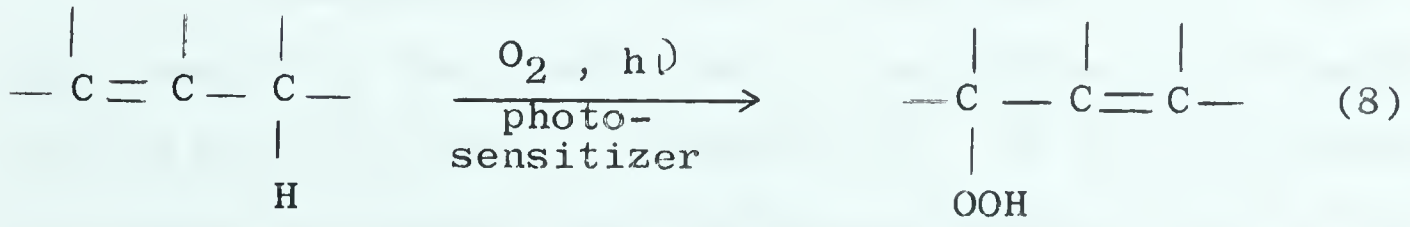
CVIII

equation 7. Epoxidation and hydrolysis of CVIII would lead to the ketone L, which on treatment with base might be expected to yield the hydroxy-ketone LI.



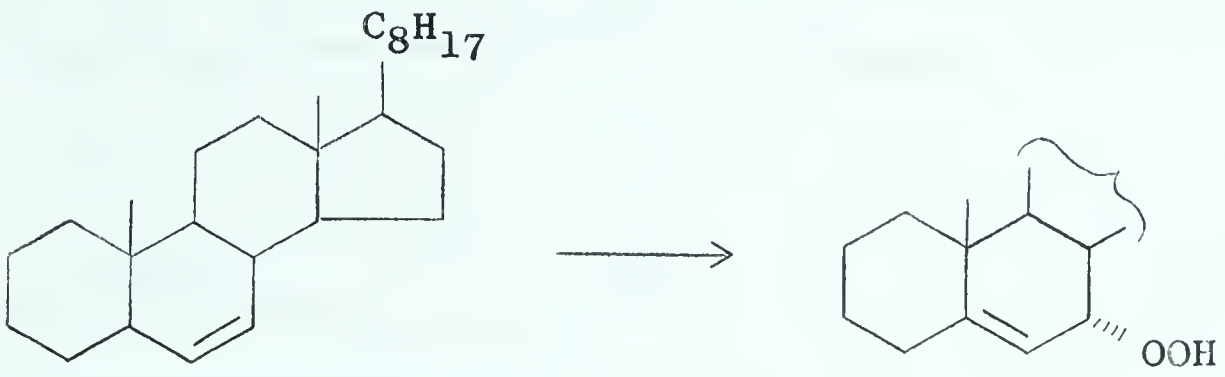
CVIII L LI (7)

A reaction which is finding increasing use as a method of introducing functionality adjacent to a double-bond is the photosensitized allylic oxidation of olefins to form rearranged hydroperoxides. The general reaction is indicated in equation 8. In the steroid



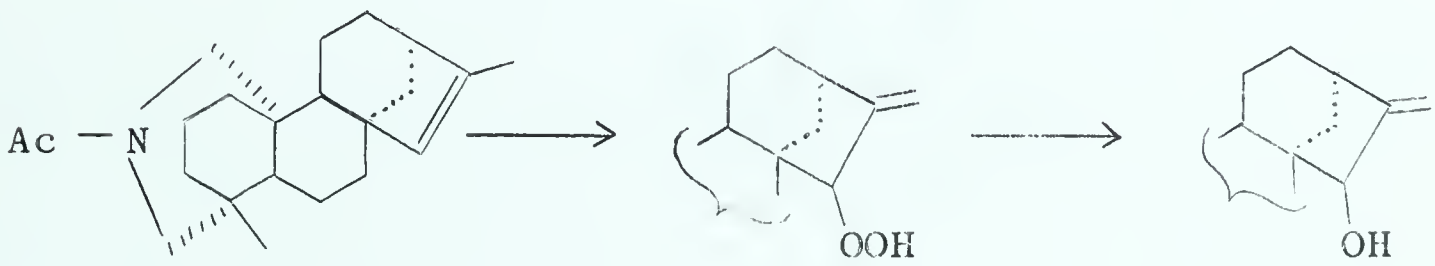
(8)

field, this reaction has been applied by Tsuda and Hayatsu (26) and by Isoe (27). An example is illustrated in equation 9. A more recent example in the field of alkaloidal natural products is provided by Masamune (28)



(9)

in his elegant synthesis of garryine. The sequence is shown in equation 10. It should be noted that in all

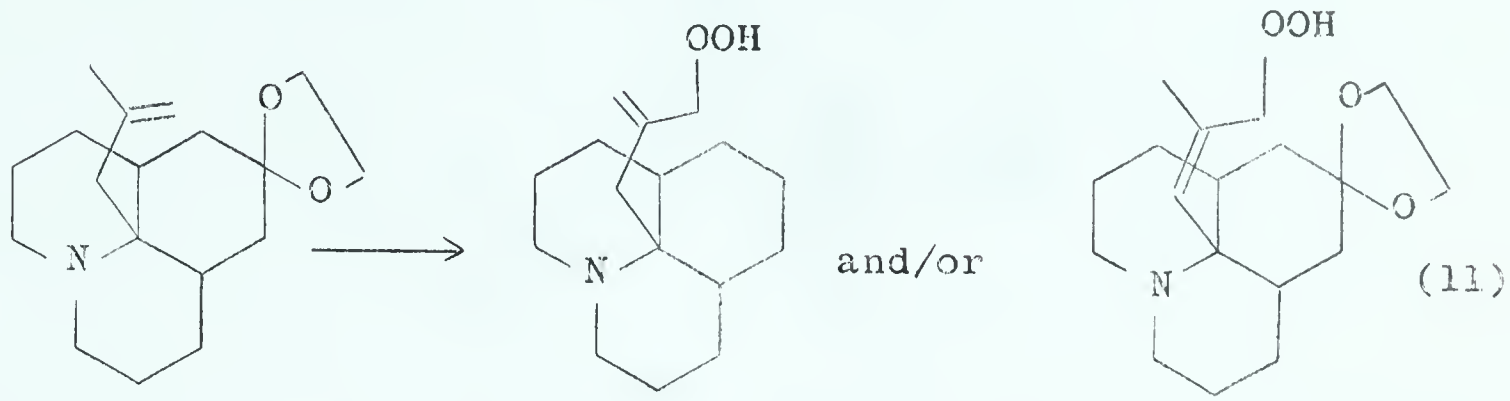


(10)

cases the double bond undergoes an allylic rearrangement.

Consideration of CVIII indicated that the reaction might result in the production of two double bond isomers LII and LIII, as shown in equation 11. It is not possible to predict in advance what the actual ratio of LII to LIII might be expected to be. The possible production of an

isomeric mixture was not regarded as a particular disadvantage however, and attempts to utilize this reaction

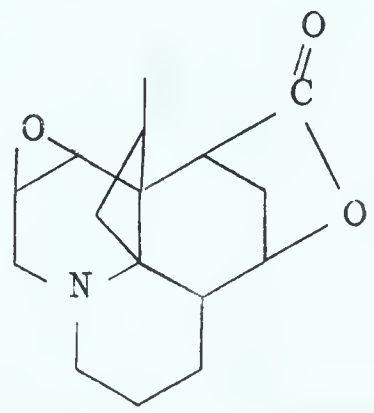


(11)

CVIII LII LIII

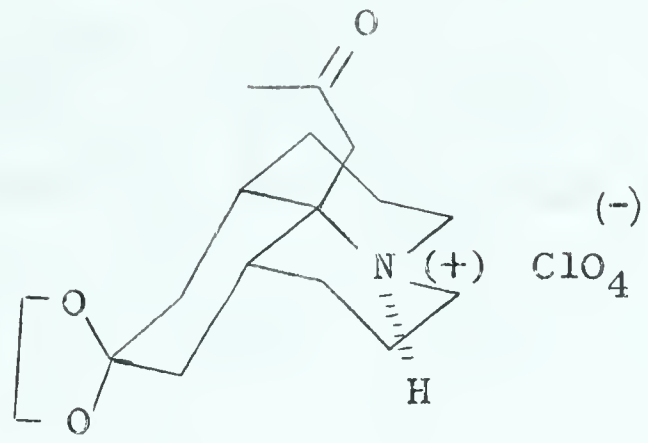
were accordingly made.

Most of the lycopodium alkaloids contain the familiar six-membered bridge-ring of lycopodine I. An exception is provided by annotinine II, which has a cyclobutane D-ring. When in the course of the present work the



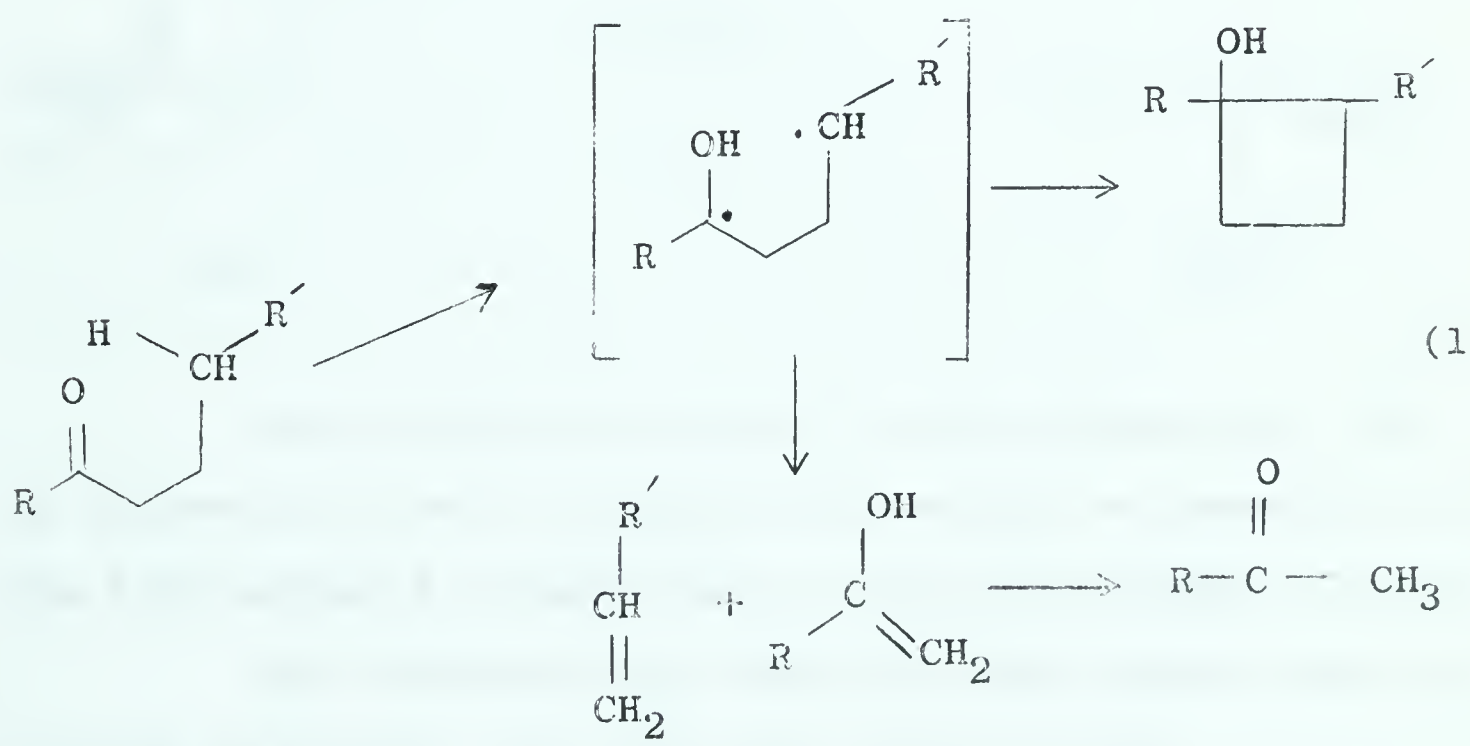
II

ketone LIV became available in reasonable amounts, interest was stimulated in attempting to form this four-membered bridge by closure of the 2-ketopropyl chain with one of the two ring-junction hydrogen atoms. Simons (29) reports that ketones carrying a side-chain with a γ-hydrogen may form



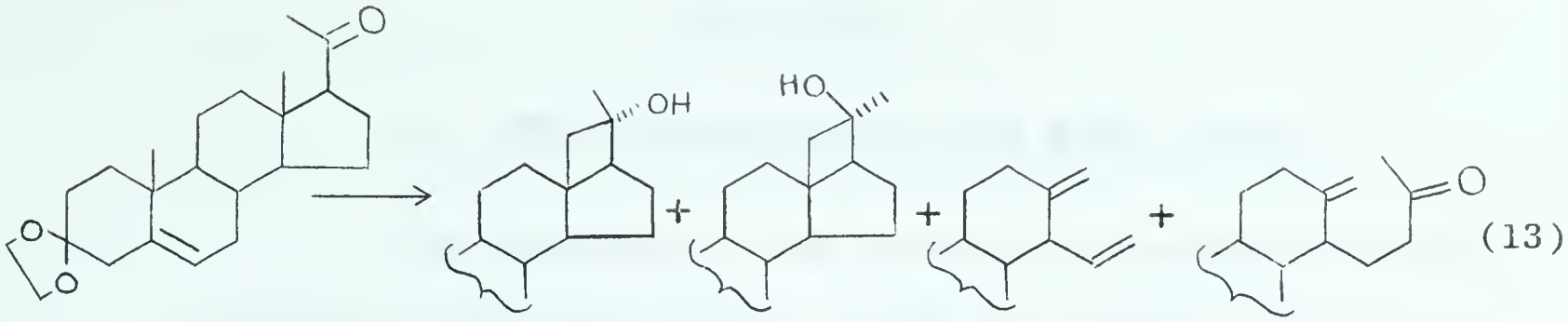
LIV

cyclobutanol derivatives on irradiation with ultraviolet light. A competing reaction is cleavage of the α,β-carbon-carbon bond of the side-chain. These reactions are indicated in equation 12. A specific example is the photolysis of nonan-2-one LV, which yields 10% of the



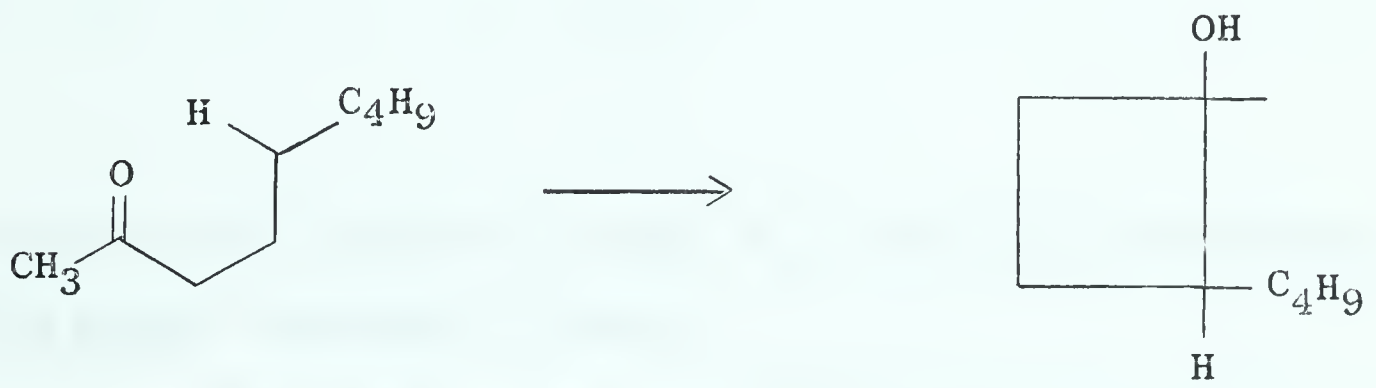
(12)

corresponding cyclobutanol LVI. An application of this reaction in sterically-restricted systems has been made by Nes (30) who carried out the photolysis of the 20-keto-steroid LVII by irradiation with a mercury arc. The reaction, together with the yields of identified products is shown



LVII 45% 3-4% 4% 24% (13)

in equation 13. The use of a restricted system has resulted in approximately 50% yields of cyclobutanols, as compared with 10% in a non-restricted system.



LV LVI

Such restriction exists in the ketone LIV, and so it was felt that a situation favourable to formation of the four-membered bridge-ring of annotinine II was at hand.

The discussion of these and other points which now follows is divided into two major sub-sections:

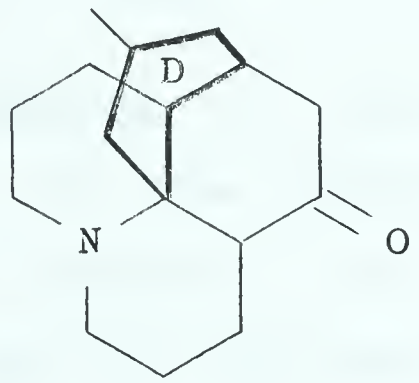
A. The Cyclohexanone-Type Model Series

B. The Julolidine Series

DISCUSSION

A. THE CYCLOHEXANONE-TYPE MODEL SERIES

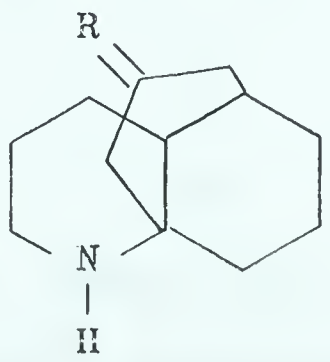
In approaching the problem of synthesis in the lycopodium alkaloid field, it was felt that the key area would be the method of formation of the bridge-ring D in lycopodine (I). It thus seemed that investigation of this



I

step in model compounds might be a desirable preliminary to the actual synthesis attempt.

The model chosen was the decahydroquinoline derivative LVIII. This compound may be regarded as being

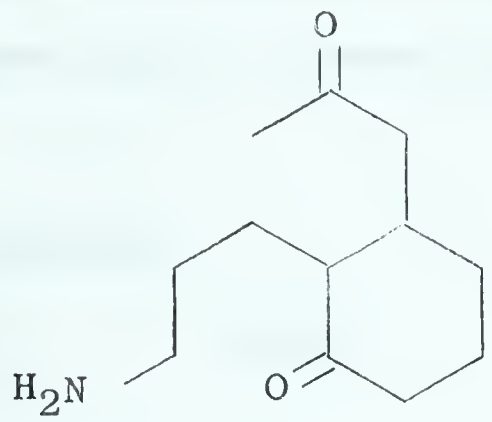


R { O (XXVI)
H, CH_3

LVIII

derived, formally at least, from the cyclohexanone derivative XXV by a type of internal Mannich reaction. It was by such an internal Mannich reaction of this compound

that we hoped to form the system LVIII. The work was

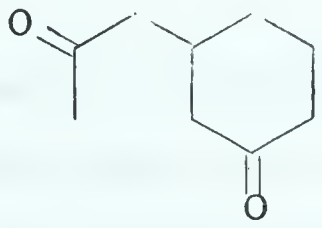


XXV

divided into four sections: (1) The formation of the 2-ketopropyl group, (2) the formation of the 3-amino-propyl group, (3) attempts to form the 2-olefin of the product from (2), and (4) the formation of N-haloamides.

1. The Formation of the 2-Ketopropyl Group

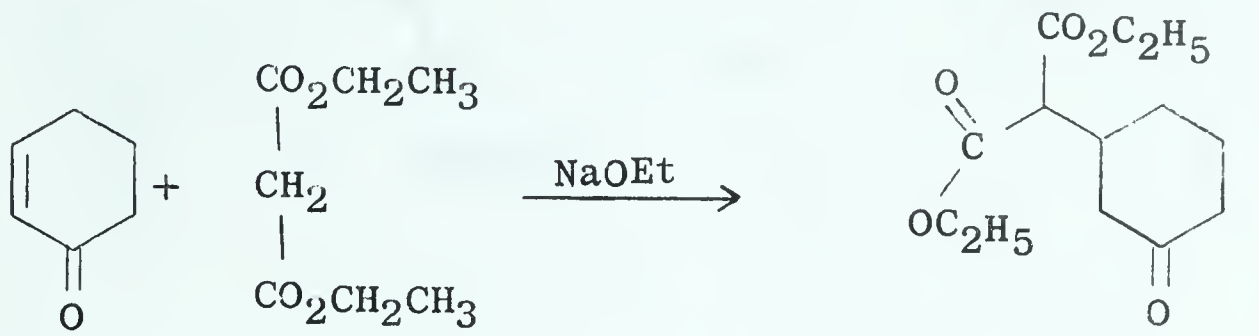
It was desired that this first stage would take the form of the synthesis of the cyclohexanone derivative LIX through the Michael addition of ethylacetoacetate to



LIX

2-cyclohexen-1-one. Westoo (31) in 1953 had carried out a Michael reaction with this ketone, using diethyl malonate, obtaining the adduct LX in 90% yield. Rabe (32) (1904) and later, Farmer and Ross (33) (1925) had reacted a 3-methyl-2-cyclohexen-1-one with ethylacetoacetate and obtained, after

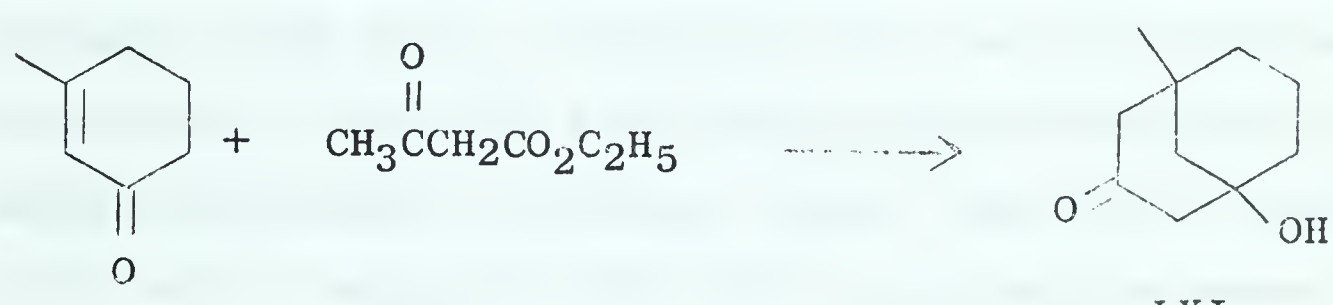
hydrolysis and decarboxylation, 1-methylbicyclo[3,3,1]-nonan-5-ol-7-one LXI in unspecified yield. In the present



(14)

LX

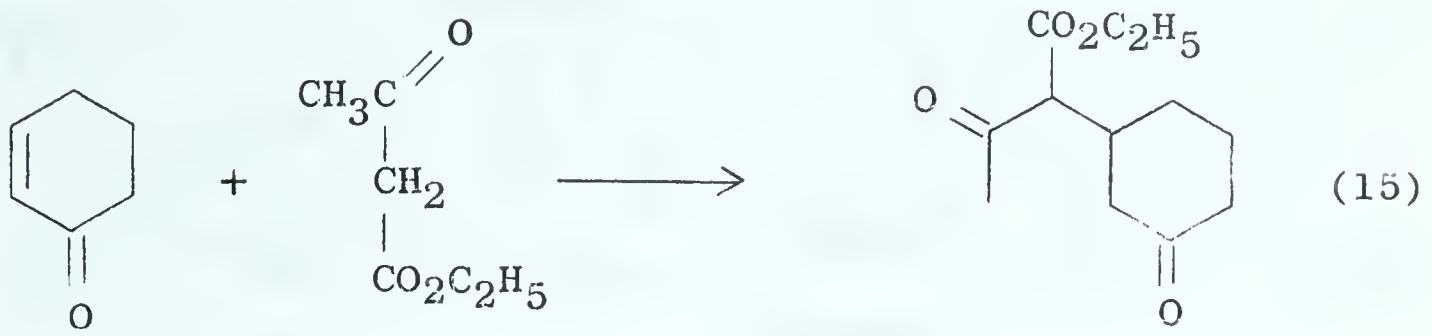
work, formation of a bicyclic product would represent a reaction carried one or two stages beyond equation 14.



LXI

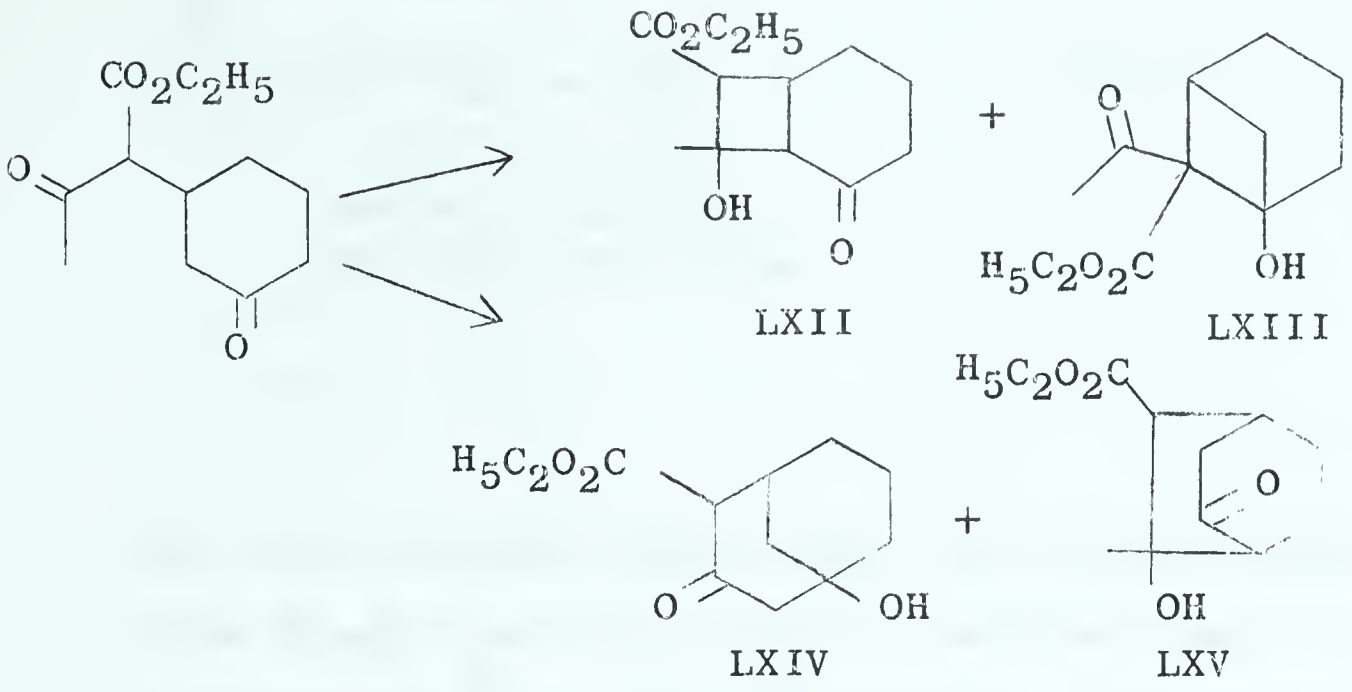
While the formation of a structure analogous to LXI would not put LIX beyond reach, yet it was felt desirable to proceed in a stepwise fashion as much as possible, and so attempts were made to isolate the products of initial reaction (e.g. LX) before loss of the carboethoxyl group took place. This initial reaction is shown in equation 15. The reaction was carried out at room temperature using as basic catalyst either sodium ethoxide or piperidine. Piperidine has been used as a catalyst in these reactions

on several occasions (34, 35). Column chromatography



(15)

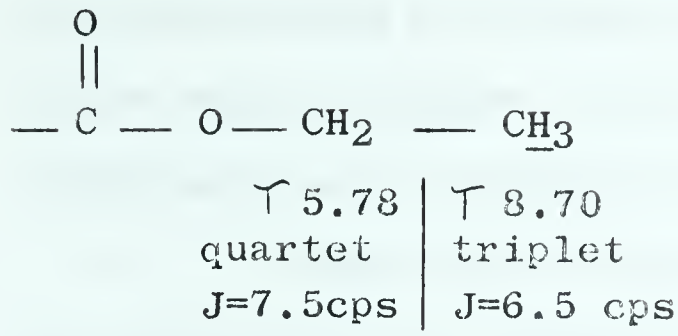
of the crude products of these reactions, which had not been treated with aqueous base, gave two main substances. The less polar of these was a crystalline solid (m.p. 136-137°) whose infrared spectrum displayed bands attributable to hydroxyl (3355 cm^{-1}), saturated ester (1730 cm^{-1}), and saturated carbonyl (1704 cm^{-1}). The more polar was only obtainable as an oil (b.p. 115-117°/0.5 mm) whose infrared spectrum displayed bands attributable to hydroxyl (3590, 3440 cm^{-1}), ester (1720 cm^{-1}), carbonyl (1700 cm^{-1}), and chelated ester (1638, 1605 cm^{-1}). Analysis and molecular weight determination on the crystalline product indicated that addition had taken place. The presence of hydroxyl absorption suggested that cyclization of the initial diketo-ester had taken place. This can be visualized as happening in several ways, as shown in equation 16. A bicyclo[3,3,1]-nonane system similar to the one shown as LXIV had already been obtained by Farmer and Ross (33) and Rabe (32). It appeared that we had obtained at least two of the four possible isomers. Assignment of structures to our synthetic products was straightforward,

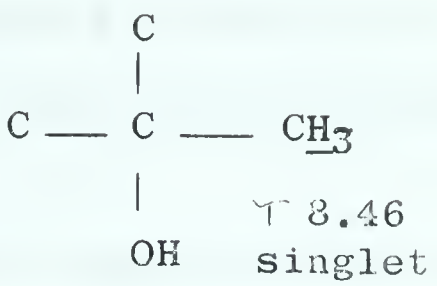


(16)

and done as follows. The presence of infrared bands attributable to a chelated ester system in the oily compound indicates that it may contain a β-ketoester group. This is supported by the fact that the oil gives a positive test with ferric chloride solution (36). This is a test for phenolic or enolic hydrogen atoms. Ethyl acetoacetate itself gives a strong positive reaction with this reagent. At the same time, the crystalline material gives a negative test with ferric chloride. Thus the structure of the oily material is undoubtedly represented by LXIV. Differentiation between LXII and LXIII on the one hand and LXV on the other as structural formulae for the crystalline ester is based on two grounds.

It was felt a priori unlikely that aldolization would take place to give a cyclobutane ring. The n.m.r. spectrum (37) of the crystalline ester shows resonance peaks assignable to the following part structures:





The usual chemical shift range for methyl protons of the type $CH_3-\overset{|}{C}-O$ is $\tau 8.6 \pm 0.2$ (38) whereas that for methyl ketones ($CH_3-\overset{O}{\overset{\|}{C}}-$) is $\tau 7.8 \pm 0.2$ (38). The appearance of the methyl signal at $\tau 8.46$ thus excludes structure LXIII. Tiers (39) lists the resonance position of the methyl group in 1-methyl-cyclobutanol LXVI as $\tau 8.70$. The lower position found in the crystalline compound may however be due to the anisotropic effects of the nearby carbonyl groups, and it

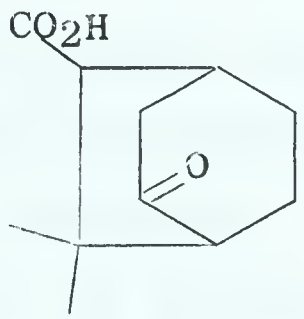


LXVI

is not safe to exclude LXII on the basis of this chemical shift data only. Since LXV is much less strained than LXII, it is felt that it probably represents the structure of the crystalline compound. It should be observed that this n.m.r. spectrum serves to distinguish between the bicyclo-[3.3.1] system and the bicyclo-[2.2.2] system. The former does not have any C - CH_3 group other than the one associated with the ethyl ester, and hence its n.m.r.

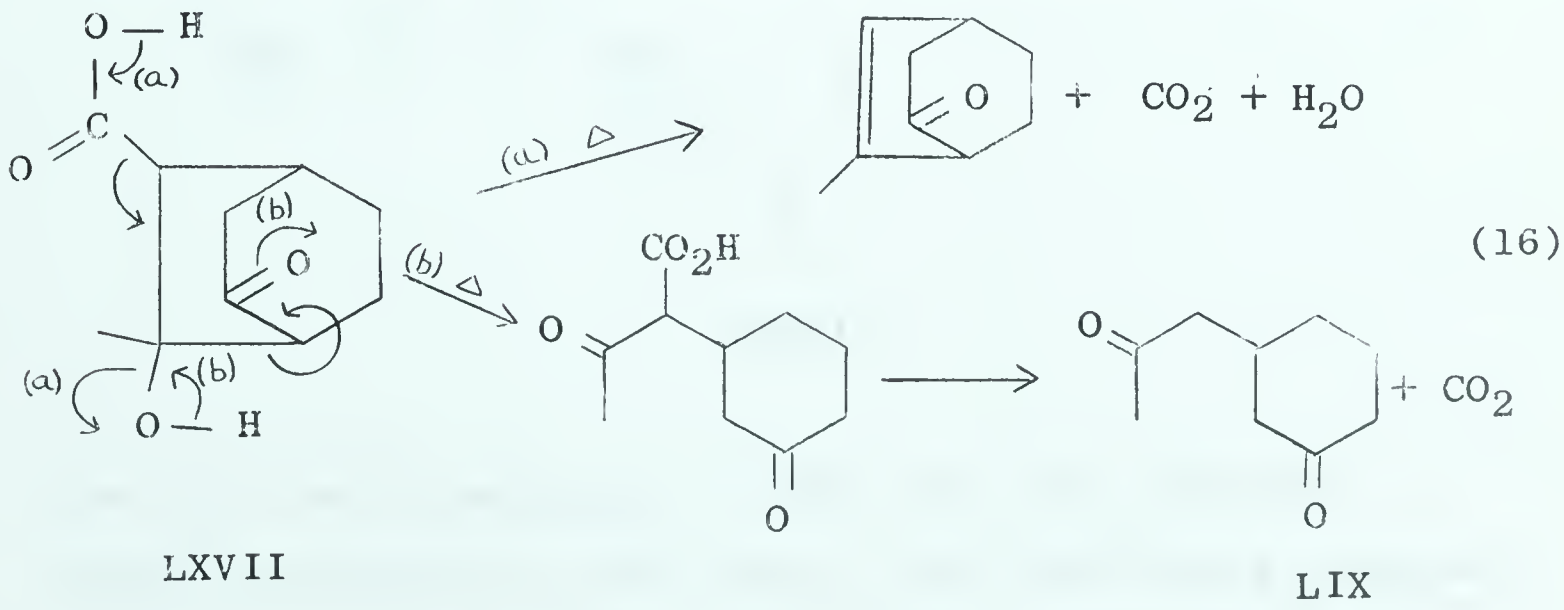
spectrum could not display any resonance attributable to other methyl groups. This means that the crystalline ester could not have the structure LXIV.

Hydrolysis of LXV with dilute aqueous alkali gave an 87% yield of a second crystalline material (m.p. 225-227° dec) whose infrared spectrum displayed bands attributable to hydroxyl (3375 cm^{-1}), carboxylic acid dimer (1710 cm^{-1}), and keto-carbonyl (1695 cm^{-1}). This is in accord with the structure LXVII. It was observed that on melting, this



LXVII

material evolved a gas and formed an oil which would not solidify on cooling. This acid LXVII can be visualized to undergo a pyrolytic reaction which evolves a gas as follows (equation 16). When this reaction was carried out on the



(16)

LXVII

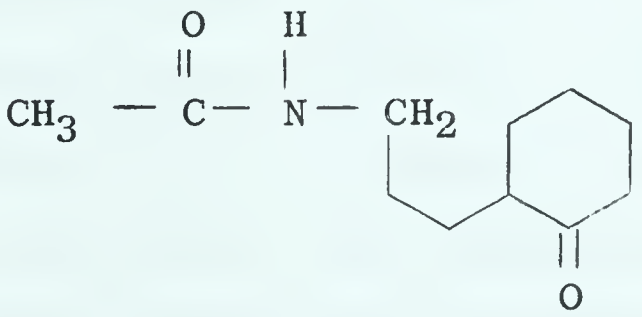
LIX

few milligrams of the acid LXVII available, there was obtained a small amount of an oil whose infrared spectrum displayed only one broad band in the carbonyl region at 1709 cm^{-1}. There was no indication of any olefinic absorption in the region 1600 cm^{-1} - 1700 cm^{-1}. Also present in the spectrum were bands at 1411 cm^{-1} (methylene adjacent to a carbonyl group) and 1355 cm^{-1} (methyl adjacent to a carbonyl group). This suggests structure LIX for this product. The fact that the absorption at 1709 cm^{-1} was broadened may indicate that the absorption bands of the two carbonyl groups are overlapping.

Having, we believed, obtained LIX, albeit in very low yield from the starting 2-cyclohexen-1-one (about 0.05%), we decided now to turn to the second phase of this problem, the introduction of the aminopropyl group.

2. The Formation of the 3-Aminopropyl Group

In this stage, it was desired to prepare the compound LXVIII. The presence of the amine protecting group

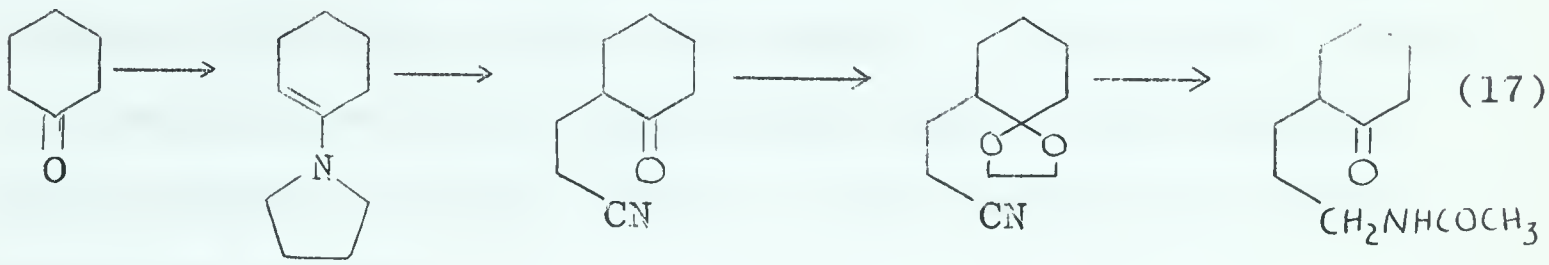


LXVIII

was felt to be desirable in that were this material to become available in good yield, then experiments designed to introduce the desired substitution at C-3 could be

examined in detail.

The synthesis was projected as outlined in equation 17. Compound LXIX had already been prepared by Stork (40), and converted to its ethylene ketal LXX by Cohen and

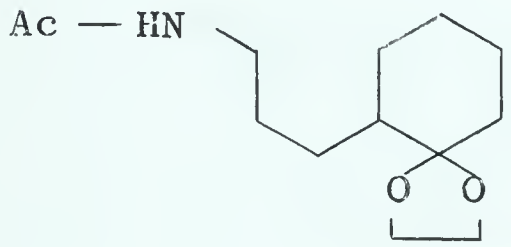


(17)

LXIX LXX LXVIII

Witkop (41). Attempts to prepare the ethylene ketal LXX by the published method (41) utilizing benzene as solvent and p-toluenesulphonic acid as a catalyst were unsuccessful in our hands. The substitution of the higher boiling solvent toluene for benzene in this reaction produced LXX on one occasion, but this could not be repeated. Several other variations were similarly failures. A method for forming these derivatives using ethylene glycol as both solvent and reagent and boron trifluoride etherate as the catalyst had been reported by Petrow et al (42). Utilizing these conditions, we were able to prepare LXX completely free of carbonyl absorption in the infrared after reaction at room temperature for 24 hours. Lithium aluminium hydride reduction (41) of LXX proceeded uneventfully and in high yield to give an oil whose infrared spectrum displayed no carbonyl or nitrile absorption. This material was then without further characterization acetylated with acetic anhydride-pyridine. The substance

obtained from this reaction was a very viscous oil (b.p. 145-149°/0.15 mm) whose infrared spectrum displayed bands attributable to an amide (3290, 3085, 1640, 1540, 1280 cm^{-1}) and an ethylene ketal (945, 920 cm^{-1}). This last assignment is an empirical one. On formation of the compound LXX these bands first appear. They are not present in the spectrum of the cyanoketone LXIX, or the N-acetyl ketone LXVIII, but are present in that of LXX, the amino-ketal and in LXXI.

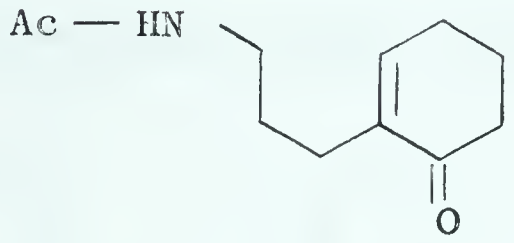


LXXI

The hydrolysis of LXXI to the N-acetyl ketone LXVIII was effected with dilute mineral acid, stirring at room temperature for twenty-four hours. This substance displayed bands in its infrared spectrum attributable to amide (3300, 3085, 1640, 1540, 1290 cm^{-1}) and carbonyl (1700, 1430 cm^{-1}) groupings. The n.m.r. spectrum of LXVIII did not display readily identifiable maxima, except for the acetyl methyl group, which gave rise to a resonance peak at τ8.01. This structural assignment was also supported by elementary analysis. The N-acetyl ketone LXVIII was thus obtained in overall yields, based on the starting cyclohexanone, ranging from 65 - 70%.

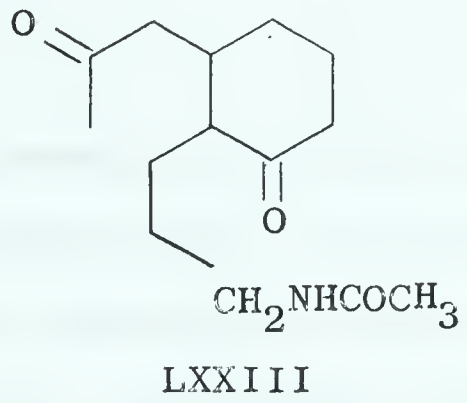
In view of the good yield of LXVIII obtainable by this route, we were encouraged to investigate the possibility

of forming the unsaturated system LXXII preparatory to introducing the 2-ketopropyl group at position 3 of LXXII



LXXII

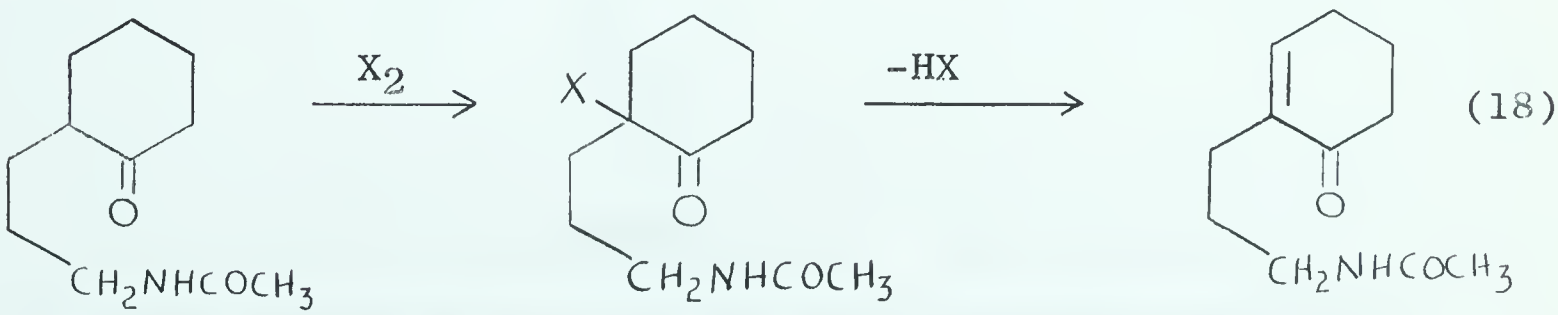
to obtain LXXIII.



LXXIII

3. Attempts to Prepare the 2-Cyclohexen-1-one LXXII

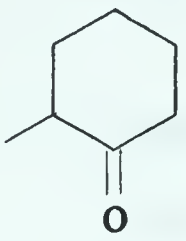
The method chosen for the preparation of LXXII is outlined in equation 18. X is a halogen atom, either bromine or chlorine. It is clear that this route requires



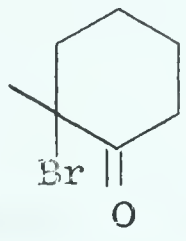
(18)

LXVIII LXXIV LXXII

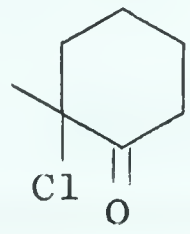
a halogenation procedure which will selectively introduce the halogen atom at position 2 and not at position 6. A satisfactory model compound for this series is found in 2-methylcyclohexanone LXXV. Corey (43) utilized this



LXXV

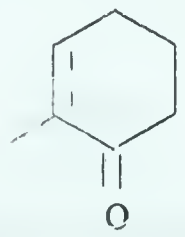


LXXVI



LXXVII

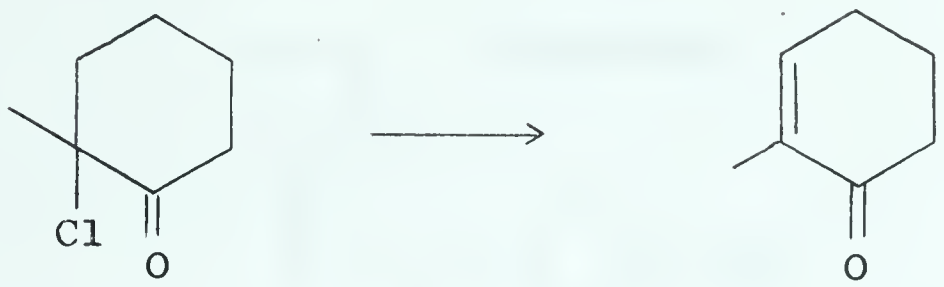
compound in the preparation of its 2-bromo-derivative LXXVI by direct bromination, assigning the axial configuration to the bromine atom on the basis of infrared spectral data (44). In addition, Johnson (45) prepared the 2-chloro-derivative LXXVII using sulphuryl chloride and LXXV. Confirmation of the position of the chlorine derives from the conversion of LXXVII to the 2,4-dinitrophenylhydrazone derivative of 2-methyl-2-cyclohexen-1-one LXXVIII. This was compared with the derivative of LXXVIII obtained by the method of Wallach (46). Johnson (45) by



LXXVIII

reactions indicated in equation 19 converted the chloro compound LXXVII to the olefin LXXVIII in 45 - 50% yield

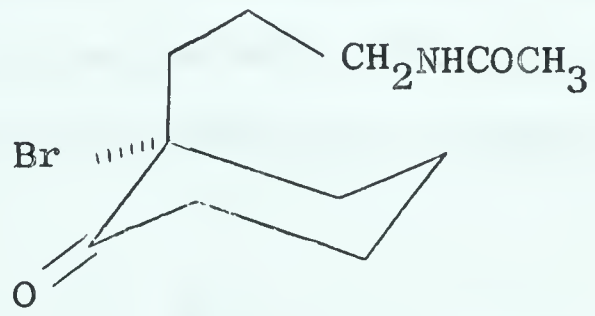
based on LXXV.



(19)

LXXVII LXXVIII

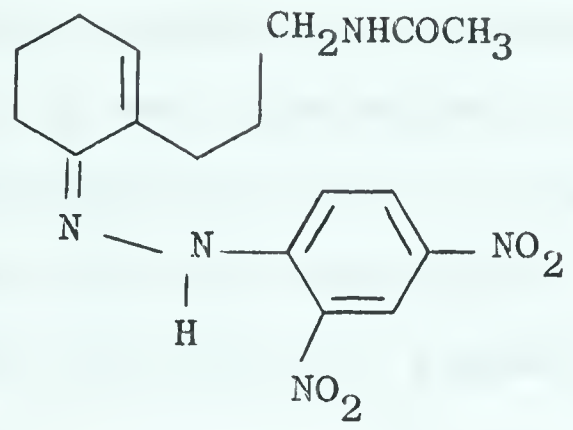
From our point of view, the situation seemed promising. Accordingly brominations were carried out on LXVIII using Corey's method (43). Material was obtained which displayed amide absorption in the infrared, unchanged from starting material. However the keto-carbonyl absorption, which in LXVIII occurs at 1700 cm^{-1}, in the bromination product had shifted to 1722 cm^{-1}. On the basis of Jones' (44) results, this clearly indicates the presence of an equatorial bromine atom, as indicated in LXXIX. Treatment of this material with 2,4-dinitrophenylhydrazine in acetic acid at 80°C for three hours



LXXIX

effected formation of a deep red crystalline 2,4-dinitrophenylhydrazone (m.p. 204-205°C.). This derivative showed strong ultraviolet absorption at 374 mμ, typical of α,β-unsaturated 2,4-dinitrophenylhydrazones (47).

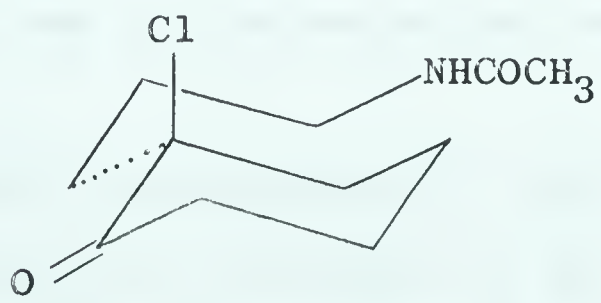
Thus this derivative is likely LXXX.



LXXX

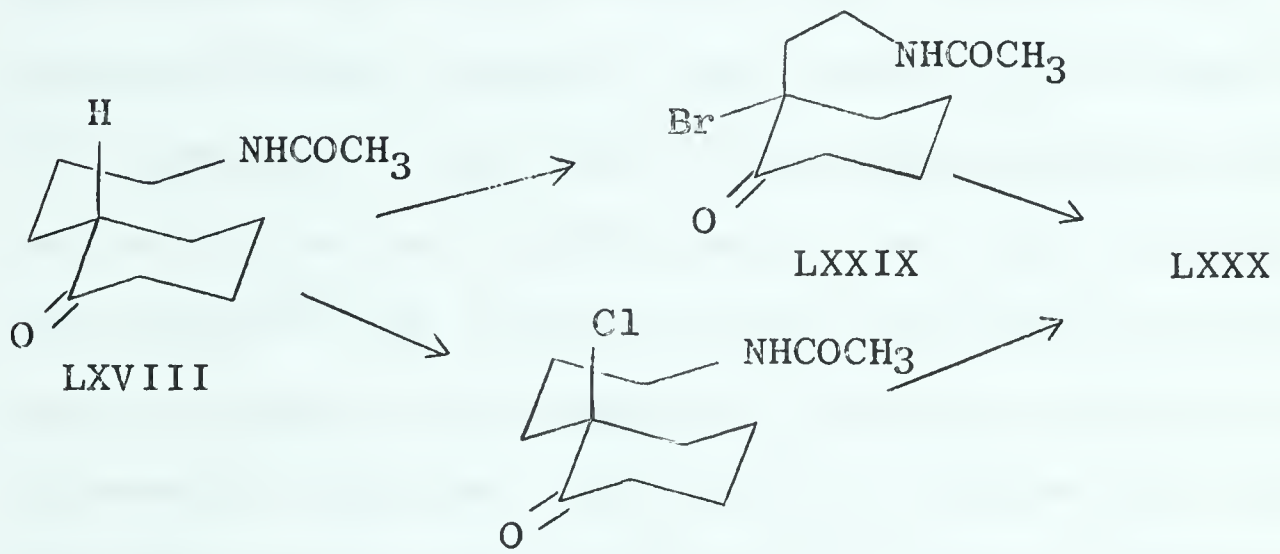
Compound LXXIX itself was very unstable, forming black gums within a few hours, even while stored in vacuo in a refrigerator.

Compound LXVIII was also subjected to a chlorination reaction using sulphuryl chloride in anhydrous carbon tetrachloride (45). Using 1-1.1 moles of sulphuryl chloride per mole of LXVIII an oil was obtained, which gave a positive Beilstein test for halogen and displayed the usual amide bands in the infrared. In addition keto-carbonyl absorption was present at 1710 cm^{-1}. This suggests that chlorination, if it has taken place, has introduced an axial chlorine, as shown in LXXXI.



LXXXI

Treatment of LXXXI with 2,4-dinitrophenylhydrazine and acetic acid under the same conditions as used for LXXIX produced a deep red crystalline derivative, whose infrared spectrum (Figure 1) was superimposable on that of LXXX, which had the same melting point, and whose melting point on admixture with LXXX was undepressed. They are thus identical. These reactions are summarized in equation 20.



(20)

LXXXI

The position now appeared favourable to carry out a dehydrohalogenation of either LXXIX or LXXXI to produce LXXII. Compound LXXXI was favoured because it is much more stable than the brominated ketone LXXIX. However, preliminary attempts using 2,4,6-trimethylpyridine (δ-collidine) or lithium bromide-lithium carbonate in dimethyl formamide on LXXXI failed to produce in the first case any δ-collidine hydrochloride, and in the second any recognizable olefinic products.

Further investigation of this approach was deferred in favour of researches in the julolidine (XXVII) series. This compound and others closely related to it appeared to lead more directly to the objective lycopodine I.

Before turning to a discussion of this aspect of the problem, it is of interest to present a side-light arising from the chlorination experiments with LXVIII.

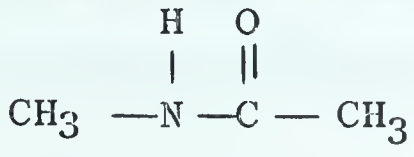
4. The Formation of N-Haloamides

The chlorination of LXVIII and the attempted dehydrochlorinations of LXXXI with γ-collidine and lithium bromide-lithium carbonate were actually performed before the formation of the unsaturated phenylhydrazone LXXX had indicated that an α-chloro-ketone had been prepared. It thus appeared for a time that the chlorination reaction had proceeded in an unexpected direction since the product apparently contained chlorine (as evidenced by a positive Beilstein test) which could not be readily removed as hydrogen chloride contrary to what is generally expected for α-chloro-ketones.

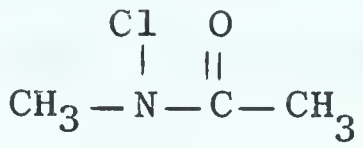
The only other centre at which one might reasonably expect to find the chlorine atom is the amide group (of LXVIII). Since it was not felt that the hydrogen atoms of the acetyl methyl group of the amide were sufficiently active to be replaced by chlorine, consideration was given to possible replacement of the hydrogen attached to nitrogen by a chlorine atom. At the time when this reaction was carried out (1961) a search of the literature failed to reveal any reference to the use of sulphuryl chloride as an N-chlorinating agent for amides. Therefore, to determine if this type of reaction could occur a model study was carried out, using N-methylacetamide LXXXII as the model

amide.

The substance was treated with sulphuryl chloride for a somewhat longer time than used for LXVIII. From this reaction a solid (m.p. 85-87°C.) which gave a positive Beilstein test was obtained in 96% yield. The n.m.r. spectrum of this solid displayed two singlet peaks of equal area at τ7.47 and τ6.99. LXXXII itself has a somewhat more



LXXXII

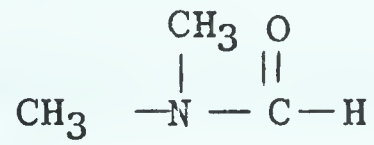


LXXXIII

complex spectrum displaying resonance maxima at τ7.99 (singlet) and τ7.22 (doublet, spacing = 5 c.p.s.). The two resonances are of equal area and the band at τ7.22 is assigned to the N-methyl protons. The fact that in the chlorination product this 7.22 peak has shifted downfield to τ6.99 indicates that the protons giving rise to this resonance have been placed in a more deshielded environment provided by the addition of a chlorine atom to the molecule. Since the peaks (7.47 and 6.99) are of equal area, the chlorine must be situated on the nitrogen. Thus the product of the reaction is undoubtedly N-chloro-N-methylacetamide LXXXIII.

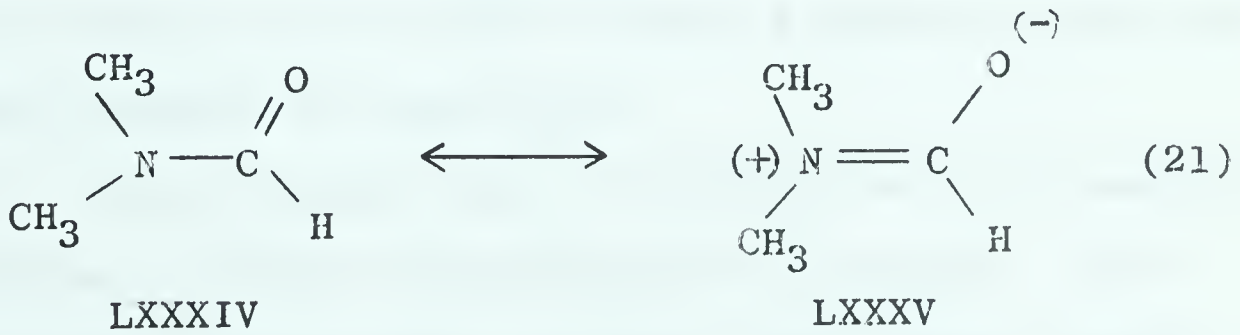
It is a well-known fact in n.m.r. spectroscopy that restricted rotation about a single bond joining two nuclei can give rise to a situation in which the various conformers created by such restricted rotation may exist

for a time long enough to prevent averaging of the shielding associated with each conformer. Under such conditions it is as though one were dealing with a mixture containing a number of components equal to the number of conformers, each at a concentration equivalent to the population of the conformer at that particular temperature. Each conformer will thus give rise to its own n.m.r. spectrum. This situation has been found to exist for the case of dimethylformamide LXXXIV (48). This substance



LXXXIV

exhibits a doublet near τ7.15 which is temperature dependent, becoming a singlet at elevated temperatures. It is thought that for this type of compound the partial double bond character of the axis of rotation, the bond connecting the nitrogen with the carbonyl carbon, is the cause of the increased stability of the rotational isomers. This is illustrated in equation 21. To the extent that LXXXV is

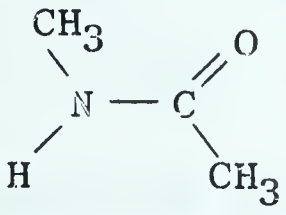


LXXXIV LXXXV (21)

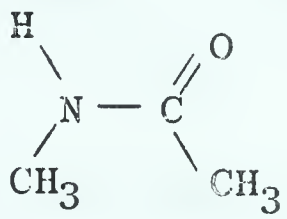
present as a conformation the methyl groups attached to the nitrogen will each experience a different electronic environment, and so give rise to resonance maxima at

different field positions.

In this way may we explain the n.m.r. spectrum of LXXXII which also exhibits a doublet, at a slightly higher field than LXXXIV, τ 7.22. The two principal rotational conformers of LXXXII are depicted below, LXXXVI, LXXXVII. The contributing resonance structures are

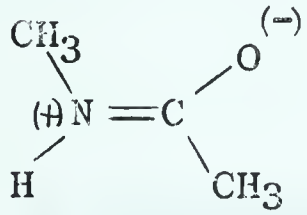


LXXXVI

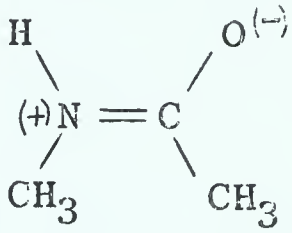


LXXXVII

illustrated by LXXXVIII and LXXXIX. Thus we expect that



LXXXVIII

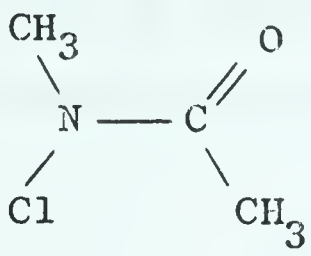


LXXXIX

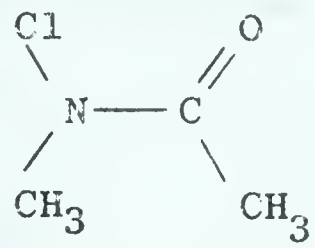
resonance due to the N-methyl protons will occur as a doublet. It might be mentioned almost parenthetically at this point that Phillips (49) does not find that the N-methyl protons are spin-spin coupled with the proton attached to the nitrogen. In fact, one must go to measurements in strong acid solution before a doublet independent of field strength is found (50).

We now recall that in LXXXIII the 7.22 resonance has shifted to τ 6.99 and collapsed to a singlet. The appearance of this singlet suggests that LXXXIII exists predominately as one of the two rotomers XC or XCI. It is unlikely that this singlet indicates unrestricted rotation about the axis since (a) resonance can still occur as

illustrated in LXXXVIII or LXXXIX, and (b) the chlorine is sterically larger than the hydrogen atom previously attached. It is considered that XC is the more likely



XC

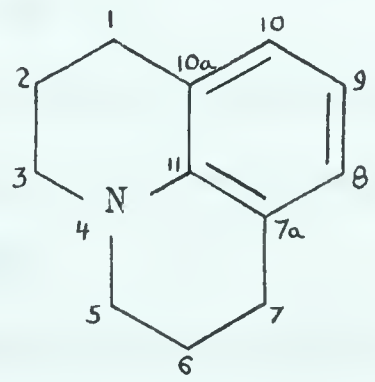


XCI

form since this is the one which has the chlorine and carbonyl dipoles oriented in opposite directions relative to each other.

B. THE JULOLIDINE SERIES

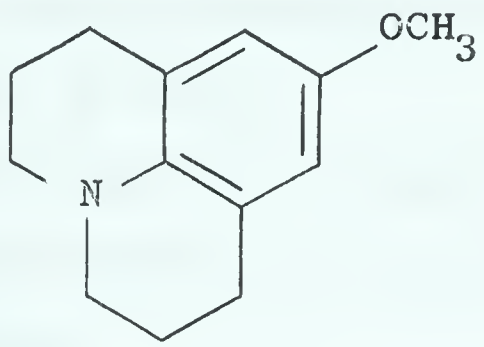
A system which is much more closely related to the lycopodine skeleton than any heretofore employed is 2,3,6,7-tetrahydro-1H,5H-benzo-[ij]quinolizine XXVII (51), commonly called julolidine. The numbering is as indicated.



XXVII

Carbons 7a, 10a, 11 are given numbers when ordinarily they would not be required since these centers will be involved

in synthetic and stereochemical discussions. The somewhat cumbersome systematic name will not be employed, the simpler term "julolidine" being preferred. The numbering as shown on XXVII will be retained for the name julolidine. For example 9-methoxyjulolidine is XXVIII.



XXVIII

It was felt that a compound such as XXVIII carrying functionality in the benzo-ring presented useful opportunities for elaboration in the desired directions. A second feature which made XXVIII attractive was its symmetry which thus provides two possible and equivalent points of attachment of the bridge-ring of lycopodine I, at either carbon 8 or 10.

The description and discussion of the work leading to XXVIII and beyond will be divided into a number of sections, as follows:

1. Preparation of XXVIII and Related Phenols.

2. The Birch Reduction of XXVIII and the Formation of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine XCIX.

3. The Grignard Reaction using Allyl Bromide and Methallyl Chloride.

4. Stereochemistry.

5. The Preparation of 9-Ethylenedioxy-11-(2-ketopropyl)-7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate CXXIII and Attempts at its Photochemical Conversion.

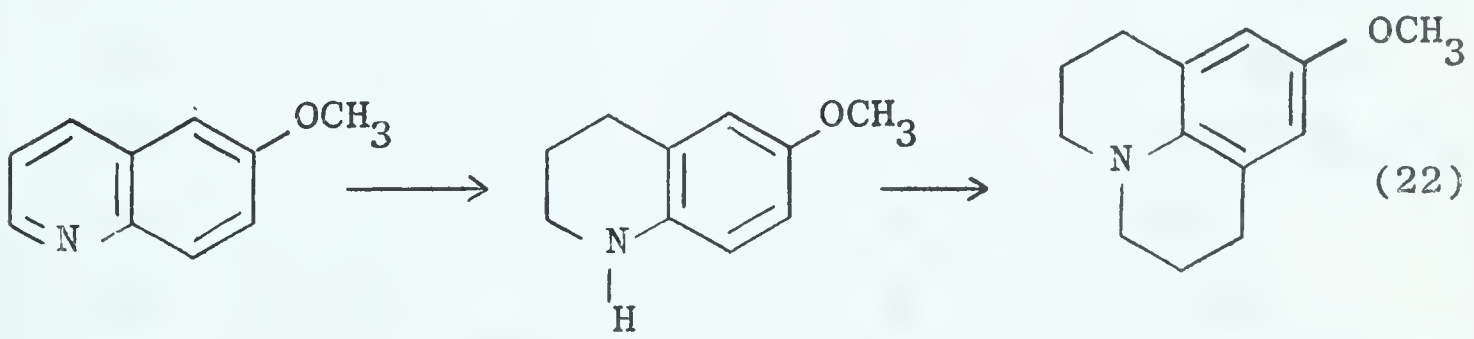
6. Reactions Involving the Olefinic Linkage of 9-Ethylenedioxy-11-methallylhexahydrojulolidine CVIII Other than Conversion to CXXIII.

7. The Introduction of Unsaturation at Carbon 7a.

8. The Mass Spectra of Representative Hexahydrojulolidine Derivatives.

1. The Preparation of 9-Methoxyjulolidine XXVIII and Related Phenols.

The scheme whereby the desired XXVIII was to be prepared is indicated in equation 22. Both 6-methoxyquinoline XCII, and 6-methoxy-1,2,3,4-tetrahydroquinoline



(22)

XCII XCIII XXVIII

XCIII are known and commercially available. The latter substance is called thalline, and is obtainable only at relatively great expense. It was therefore desired to prepare XXVIII using the much more available and less

expensive XCII.

The quinoline XCII when treated with hydrogen at medium pressure in the presence of Adams' catalyst readily underwent hydrogenation. The experimental conditions eventually developed (hydrogen pressure 50 psi, 10% w/w Adams' catalyst) gave a single reduction product. Assignment of structure XCIII to this product was made on the basis of n.m.r. analysis. The substance obtained from the reduction was an oil (b.p. 101-102°C./0.5 mm) or a low-melting solid whose n.m.r. spectrum displayed bands readily interpretable in terms of XCIII. These, together with assignments, are shown in Table 1. The band at τ6.53 can

Table 1

NMR Spectrum of Thalline XCIII in Carbon Tetrachloride

Band Position, τ	Intensity	Multiplicity	Assignment
8.23	2	m	$-CH_2-CH_2-CH_2$
7.36	2	t	$Ar-CH_2-CH_2$
6.90	2	t	$Ar-NH-CH_2-CH_2$
6.53	1	s	$-NH-$
6.38	3	s	$-O-CH_3$
3.63	3	m	Aromatic ABX

be assigned to the proton attached to nitrogen, since this resonance disappears when the sample is shaken with deuterium oxide, and the spectrum remeasured. This spectrum as shown in Table 1 is exactly what would be expected for thalline

XCIII, and thus this structure is assigned to the reduction product.

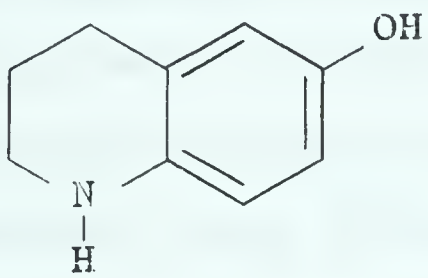
In addition of course, the physical constants of the synthetic material and its hydrobromide salt were in agreement with the literature values (52).

An interesting feature of this reaction is that, using the conditions indicated above, there was no evidence of any over-reduction. One reaction was allowed to proceed for 157 hours at 50 psi and gave a quantitative yield of thalline.

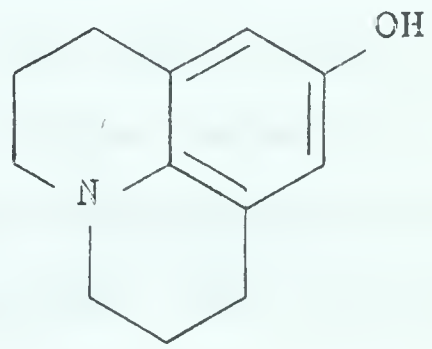
Turning now to the second step of this sequence, the formation of 9-methoxyjulolidine XXVIII, the preparative method utilized was that reported (53) for julolidine XXVII itself. This involved refluxing a solution of the corresponding tetrahydroquinoline in sufficient 1-bromo-3-chloropropane to act as both reagent and solvent, for about one day and then isolation of the julolidine XXVII by standard methods. For the preparation of XXVIII this procedure was used essentially unchanged. It was found however, that yields were materially reduced if the reflux time was extended appreciably beyond 18 hours, or if fresh (either new or recently redistilled) 1-bromo-3-chloropropane was not used. In this way yields of XXVIII ranging from 50-70% were obtainable. Here, as in the case of XCIII, n.m.r. analysis played the major role in structural assignment, and the spectrum is reproduced in Figure 11. This spectrum is exactly in accord with what would be predicted for a compound of structure XXVIII. Furthermore, the spectrum remained unchanged after exchange with deuterium

oxide, indicating the absence of any readily exchangeable protons, and hence the absence of any hydrogen bonded to nitrogen. In addition the structural assignment is supported by elementary and mass spectral (Figure 20) analysis.

Having thus developed a route to XXVIII which proceeded in good overall yield, it was also desired to prepare the phenols corresponding to XXVII and XXVIII, namely 6-hydroxy-1,2,3,4-tetrahydroquinoline XCIV, and 9-hydroxyjulolidine XCV.

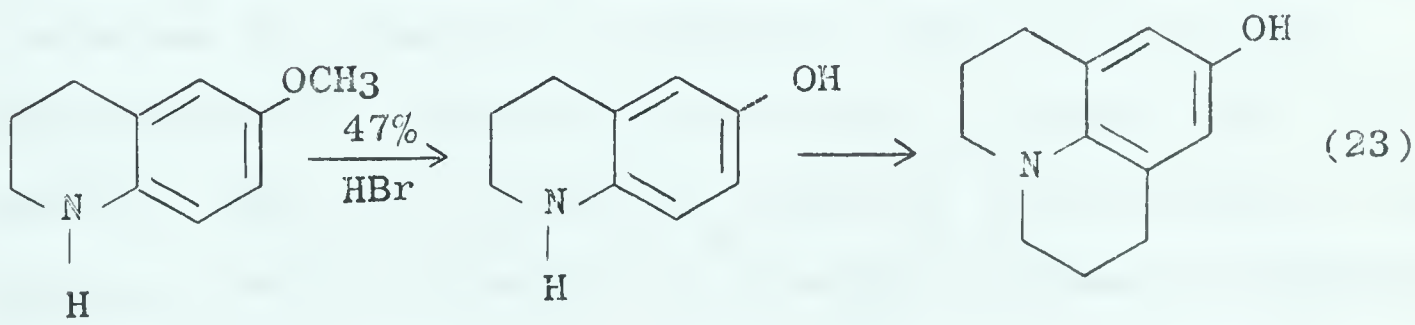


XCIV



XCV

The method chosen for the preparation of these two phenols is shown in equation 23. Treatment of XCIII



(23)

XCIII XCIV XCV

with constant boiling hydrobromic acid at the reflux temperature for 4-6 hours led to the isolation of a material

insoluble in the reaction medium whose infrared spectrum was characteristic of a phenol (3240 cm^{-1}) and the hydrobromide salt of an amine (2750 cm^{-1}, broad). This salt (m.p. 153-154°C.) was obtained in 55% yield. Conversion of this salt to the base yielded the crystalline amino-phenol XCIV, m.p. 147-149°C. The reported (54) melting point for this compound is 148°C. The n.m.r. spectrum as determined in trifluoroacetic acid displayed broad bands corresponding to two protons each at τ 8.1, τ 7.38, and τ 6.6. It also showed resonance in the aromatic region at τ 3.25 (multiplet) corresponding to three protons. There was as well a low broad band at τ 1.58 of about 2.5 protons intensity. The resonance present in XCIII at τ 6.38 and assigned to the methoxyl group protons had disappeared. This material is thus the desired phenol XCIV.

When this phenol XCIV was treated with 1-bromo-3-chloropropane at reflux temperature a crystalline substance separated and was collected by filtration. The infrared spectrum (nujol mull) of the crystalline material indicated the presence of hydroxyl (3210 cm^{-1}) and the hydrobromide or hydrochloride salt of an amine (2600 cm^{-1}, broad). The n.m.r. spectrum, again in trifluoroacetic acid, showed a series of bands very similar to those corresponding to XCIV. In the aromatic region there was, however, a new band at τ 3.55. Assuming that this can be associated with the aromatic protons of XCV, the integration curve of this spectrum indicates the presence of about 60% of the desired XCV. Conversion of this mixture of salts to the bases

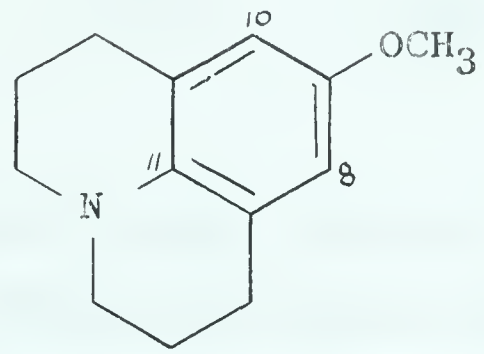
followed by chromatography did not readily effect their separation. When, however, the crude bases were treated with perchloric acid to form the corresponding derivative, the solid perchlorate obtained displayed only a single band at τ 3.6 in the n.m.r. spectrum (Figure 12). In this way, 94% of the estimated 60% yield of XCV could be recovered. The mass spectrum (Figure 21) of the phenol thus obtained displayed a peak at m/e 189, the position to be expected for the parent peak of the phenol XCV, which completed the evidence necessary to assign firmly the structure XCV to the compound.

2. The Birch Reduction of XXVIII and the Formation of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine XCIX.

One of the features of major interest in any synthetic attempt on lycopodine or any of the family possessing the same skeleton is, as mentioned in Part A, the development of a sequence leading to the formation and elaboration of the bridge-ring of that compound. The major part of the work devoted to the julolidine series and reported here has been directly concerned with this.

It was visualized that the problem could best be dealt with in two stages. These are (a) the addition of a chain of carbon atoms, containing an easily elaborated functional group, to XXVIII or a suitable modified form of it, and (b) closure of the ring. Considering the structure XXVIII, it is apparent that the bridge-ring will have its

points of attachment to the julolidine skeleton at carbon 11 and either carbon 8 or carbon 10. This section describes



XXVIII

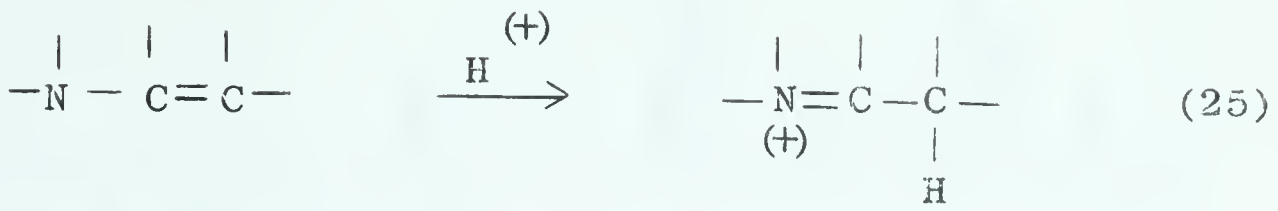
the development of a structure which will provide a suitable reaction centre at carbon 11 so that one end of the bridge may be readily attached there.

It is well known (55) that structures of the type -N=C- are readily attacked by nucleophilic alkylating agents, with the resultant formation of a new bond to carbon, as indicated in equation 24, where R is a suitable



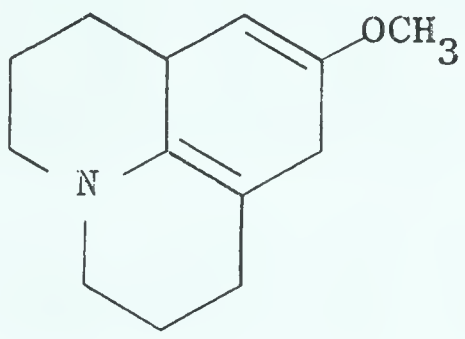
(24)

nucleophilic reagent. It was felt that a method of this type would have to be applied in this series, since reactions at carbon 11 of XXVIII are not expected to be facile. Since it is also known (24) that isomerizations of the type shown in equation 25 are readily brought about, dissolving metal reduction of XXVIII appeared to be the best first attempt to obtain the desired modification of XXVIII.



(25)

The reduction product desired from this reaction was 9-methoxy-8,10a-dihydrojulolidine XXXVI. The identification of this substance among the products of the



XXXVI

reaction was not expected to be difficult for the following reasons. Firstly, the protons attached to the vinyl methoxyl group in XXXVI should display absorption in the n.m.r. spectrum at somewhat higher fields than do the corresponding protons in XXVIII, and the enol-ether as a function should display a strong band in the infrared region at about 1650 cm^{-1}. Secondly, although the enamine function will not be directly detected by n.m.r. measurements, it should display infrared absorption near 1630 cm^{-1}, which should show a shift to higher frequency on formation of a salt (24) in accordance with equation 25.

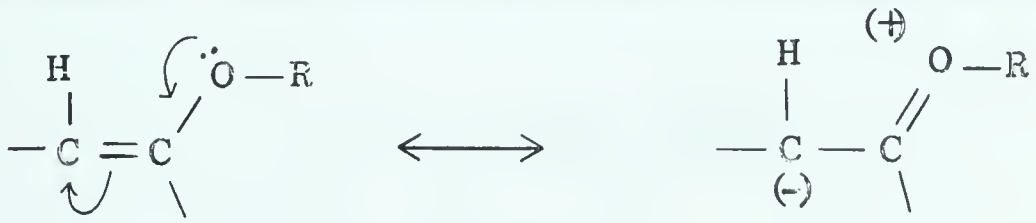
Development of suitable conditions for this reaction proved to be one of the most difficult and time-consuming

Table 2

Birch Reduction of 9-Methoxyjulolidine XXVIII

Metal	Solvent	Co-solvent	Proton Source	Time min.	Ratio Metal to Substrate (equiv.)	%	Products Name	Spectral Data Infrared cm^{-1}	NMR
Li	NH_3	Et_2O	EtOH	30	1/1	48 52	an enol ether starting material	1645 -	6.58 6.38, 3.78
Li	NH_3	Et_2O	EtOH	60	1/1	48 52	enol ether starting material	- -	6.5 6.29
Li	NH_3	Et_2O	EtOH	240	30/1	38 62	enol ether starting material	1660 -	6.58 6.39
Na	NH_3	Et_2O	t-BuOH	100	0.62/1	0 100	enol ether starting material	- -	- 6.32, 3.70
Li	NH_3	p-dioxan	EtOH	120	3.2/1	20 25	phenol ? phenol ?	3380,1660 3380,1645	8.85 8.35, 7.38 6.15
Li	NH_3	Et_2O	EtOH	120	2/1	45 55	enol ether starting material	1660 -	6.58 6.38, 3.8
Li	N_2H_4	Et_2O	EtOH	570	1/1	100	?	1720,1700 1680	8.9, 8.8
Li	NH_3	Et_2O	t-BuOH	50	1/1	64 36	enol ether starting material	1650 -	6.58 6.38, 3.8

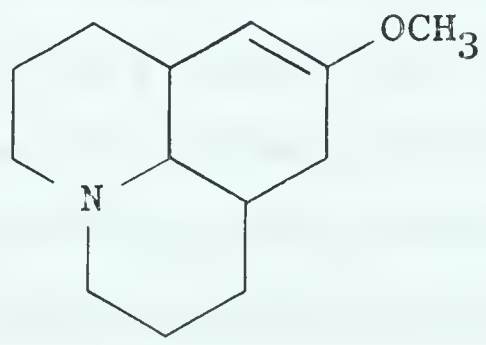
aspects of the whole problem. The various conditions, etc., tried are summarized in Table 2. As a rule the products of reduction were isolated by evaporation of the amine solvent, taking up the precipitated salts in water, and extraction of this aqueous mixture with ether or petroleum ether. Evaporation of the extract yielded the crude reaction mixture from which the spectral data recorded in Table 2 were obtained. Thus in the n.m.r. spectra of most of these product mixtures, a sharp signal at τ 6.58 was suggestive of an enol-ether grouping. Also present, although not recorded in Table 2 was a resonance maximum at τ5.85, one-third of the intensity of the peak at τ6.58. This was associated with the β-proton of the enol-ether (the proton on carbon 10 of XCVI). It should be noted that such vinyl protons are found at abnormally high fields for olefinic protons (48, p.62) presumably because the electron density at the proton is increased by resonance effects as indicated below. The infrared spectra of these mixtures



showed a band at 1645 cm^{-1}, attributable to enamine and/or enol-ether absorption. All this evidence is compatible with both structures XCVI and XXXVI. The feature which indicated that possibly the reduction product might not be the desired XXXVI was that on forming perchlorate

derivatives of the product mixture, there was no evidence of a change in the corresponding infrared spectrum ascribable to the type of isomerization shown in equation 25, that is, a shift of a band to or an appearance of a band in the vicinity of 1680 cm^{-1} (24).

The reaction mixture was subjected to short path vacuum distillation which provided a colourless oil (b.p. 71°C./0.07 mm) displaying no resonance in its n.m.r. spectrum in the region associated with aromatic protons. The distillate thus contained no starting material XXVIII. Measurement of the mass spectrum of this oil should now serve to demonstrate the presence of XCVI and/or XXXVI since the parent peak of the former should appear at m/e 207 and the latter at m/e 205. When the spectrum (Figure 24) was actually determined a strong peak at m/e 207 appeared, together with a very weak one at m/e 205. There was no peak at m/e 203, corresponding to XXVIII. The reaction product was thus one of over-reduction containing an enol-ether. Its structure must therefore be XCVI.

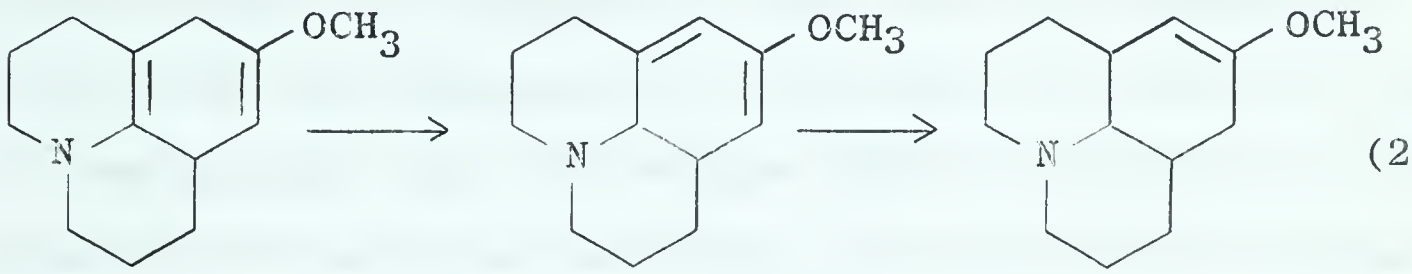


XCVI

It is obvious now why the presence of the enamine was not revealed on salt formation. The mass spectrum of XCVI

will be discussed in more detail in a subsequent section.

The reason for this facile over-reduction was not at once apparent, since one would not expect XXXVI, containing as it does two isolated double bonds, to undergo ready Birch reduction. It was considered feasible that if the dihydro compound XXXVI were in extended contact with lithium or even lithium amide in ammonia solution, a rearrangement to a conjugated diene could occur, followed by further reduction as shown in equation 26. In order to



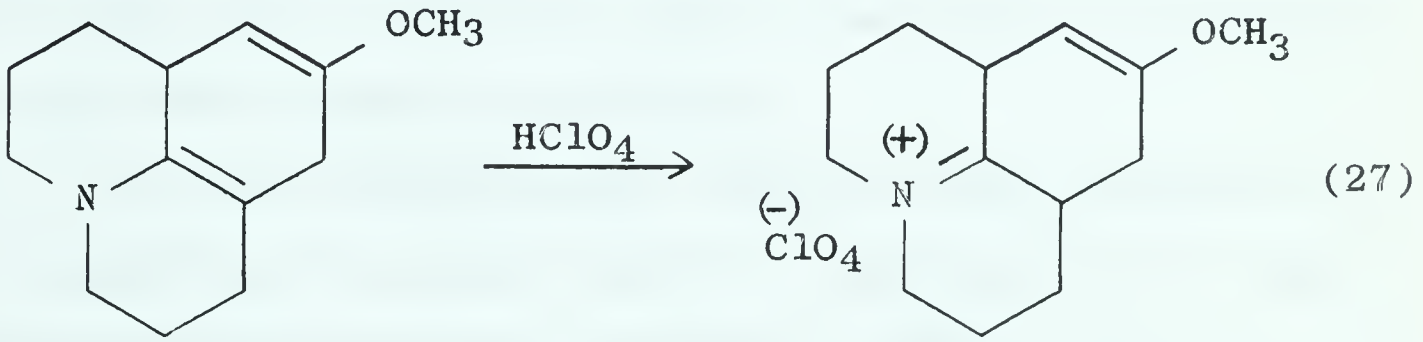
(26)

XXXVI XCVI

minimize this contact time, it was desired to destroy the lithium-organic substrate complex of the dihydro form XXXVI as fast as it formed. To do this effectively, the proton source should be present while reduction is taking place. Thus the use of t-butanol is indicated instead of ethanol. It was also felt that a metal less reactive than lithium, such as sodium, would further reduce the likelihood of rearrangement and subsequent over-reduction. These two variations were incorporated in the fourth attempt and gave a good recovery of starting material. There was no evidence of any reduction.

The next three attempts rejected sodium and t-butanol altogether, and in the one case where a recognizable reduction product was isolated, gave only the tetrahydro compound XCVI.

The aversion to the use of t-butanol having been overcome, a run was made using it in combination with lithium. This time a 64% yield of a material with the expected spectral characteristics was obtained. This product, unlike the others, however, displayed a shift in the infrared spectrum on salt formation in accord with expectations. In conjunction with the n.m.r. spectrum indicating the presence of an enol-ether by a band at τ 6.58, it was apparent that the desired XXXVI was finally at hand. Equation 27 indicates the change occurring on salt formation.



(27)

enamine 1650 cm^{-1} — iminium perchlorate 1680 cm^{-1}

XXXVI — XCVII

During the course of the research as this experiment was repeated to obtain further XXXVI, it soon became apparent that a problem remaining to be cleared up was the variable yields of XXXVI resulting from the reduction. These ranged from 0-80% seemingly at random. It has been reported (22) that the presence of small particles of iron

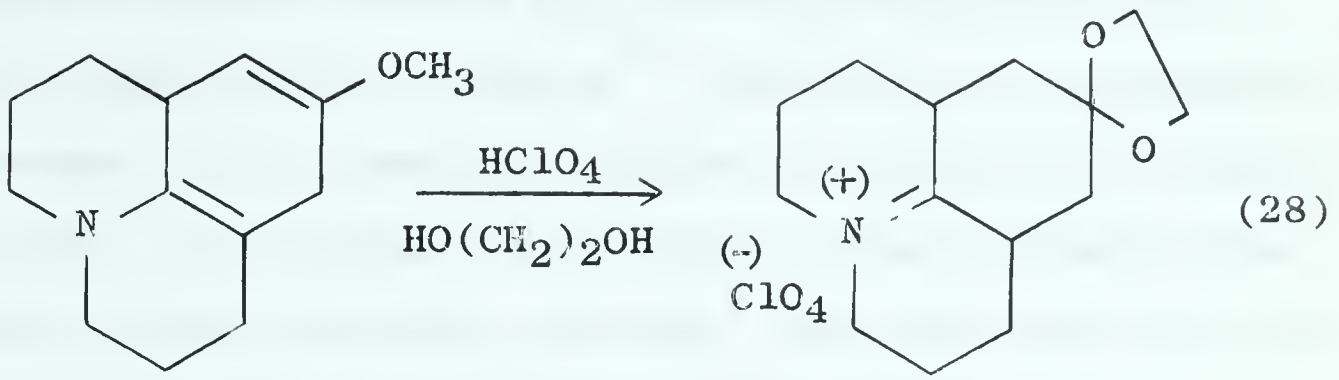
in liquid ammonia dispensed from iron cylinders interferes with the formation of lithium complexes by catalyzing the reaction of the metal with the proton donor. This can be overcome by redistilling the ammonia before use. In the case of the present reduction, when ammonia was used which had been redistilled immediately before use, reproducible, almost quantitative yields of XXXVI could be obtained.

The 9-methoxydihydrojulolidine XXXVI is an oil, unstable in air. Its n.m.r. spectrum displays bands attributable to methoxyl protons (τ6.58) and a vinyl proton (τ5.48). The infrared spectrum shows absorption at 1645 cm^{-1} attributable to overlapping enamine and enol-ether frequencies. Formation of the perchlorate salt of XXXVI gave colourless crystals, whose infrared spectrum (Figure 2) showed strong absorption at 1679 cm^{-1} and a shoulder on this band at 1638 cm^{-1}. These are due to the iminium perchlorate and vinyl ether groups respectively.

As has been mentioned, XXXVI is very unstable in air, decomposing to a deep red oil. Investigation of this decomposition yielded some unexpected results. In the specific case which was examined, reduction of XXVIII had yielded a product mixture containing 70% unreduced XXVIII and 30% XXXVI, as indicated by the n.m.r. spectrum of the mixture. This particular spectrum, measured in carbon tetrachloride solution, displayed resonance at τ6.40 (relative integrated peak area 11) associated with the protons on the methoxyl group of XXVIII, at τ6.55 (relative integrated peak area 5) associated with the protons on the methoxyl

group of XXXVI and at τ 5.5 (relative integral peak area ca 2), associated with the vinyl proton on carbon 10 of XXXVI. When this spectrum was remeasured some time later, it was found that these latter two peaks had disappeared. It is felt that this change in the spectrum represents a reversion of XXXVI to XXVIII, presumably by aerial oxidation of the dihydro-aromatic ring of XXXVI. In view of the time and effort expended in obtaining the compound, this was a situation which had to be remedied.

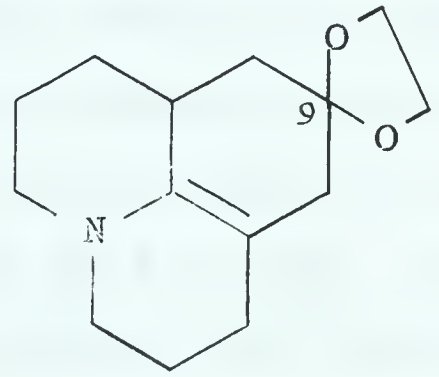
Difficulties of this type had not been experienced with XCVI, and it was thus felt that the solution to this problem lay in removing at least one of the two olefinic linkages in the cyclohexane ring of XXXVI and at the same time preserving the essential enamine linkage. This could be done by the simple expedient of forming the perchlorate salt XCVII; however previous attempts at this had always resulted in considerable hydrolysis of the enol-ether. If another carbonyl blocking group, more insensitive to acid than the enol-ether, could be used to replace this function, formation of the corresponding iminium perchlorate should prevent the decomposition. An ideal such blocking group appeared to be an ethylene ketal. Since enol-ethers are readily hydrolyzed by strong acid, there appeared to be a possibility of carrying out a "trans-derivatization" and forming an iminium perchlorate salt simultaneously by treating XXXVI with ethylene glycol in the presence of excess perchloric acid. Equation 28 indicates the reaction involved. XCVIII as written is really a derivative of XCIX,



(28)

XXXVI XCVIII

a tetrahydro julolidine, and as such should not undergo ready aerial oxidation. Such oxidation is further inhibited by the presence of a quaternary centre at carbon 9.



XCIX

When the crude reduction product was dissolved in ethylene glycol containing excess perchloric acid there was obtained almost at once a precipitate. This precipitate was digested in boiling methanol for some time to remove any ethylene glycol adhering to the solid material. The infrared spectrum (nujol mull) (Figure 3) of the resulting colourless crystals (m.p. 241-242°C., dec) displayed absorption at 1670 and 1080 cm^{-1}, indicating the presence of an iminium perchlorate. Conversion of this salt to the

free enamine by treatment with saturated aqueous sodium carbonate gave a reddish oil, whose infrared spectrum showed absorption at 1642 cm^{-1}, indicative of an enamine and whose n.m.r. spectrum (Figure 13) displayed a singlet at τ 6.12. This signal is assigned to the ethylene ketal protons on the following grounds. The relative peak area of the 6.12 band is very nearly 4/21 of the total integrated peak areas. Since XCIX contains 21 protons, the signal in question must therefore represent 4 protons, indicating the ethylene ketal. In addition Kalvoda and co-workers (56) report that resonance associated with ethylene ketal protons generally occurs at τ 6.1 $\pm$ 0.1. The band is also well shifted from the band caused by the methoxyl protons of 9-methoxyjulolidine XXVIII (τ 6.39), 9-methoxydihydrojulolidine XXXVI (τ 6.52), and 9-methoxy-tetrahydrojulolidine XCVI (τ 6.58). Thus the perchlorate salt is the desired XCVIII, and the free base is XCIX. Structural assignment of XCVIII to the iminium perchlorate is also supported by elementary analysis.

This procedure was developed at a time when yields of XXXVI by Birch reduction of XXVIII were still variable. It was found that the bases obtained by treatment of the solid insoluble in perchloric acid-ethylene glycol with aqueous sodium carbonate contained no XXVIII as judged by the absence of any bands attributable to aromatic protons in the n.m.r. spectrum of these bases. This in spite of the fact that n.m.r. measurements of the crude Birch reduction product usually indicated the presence of

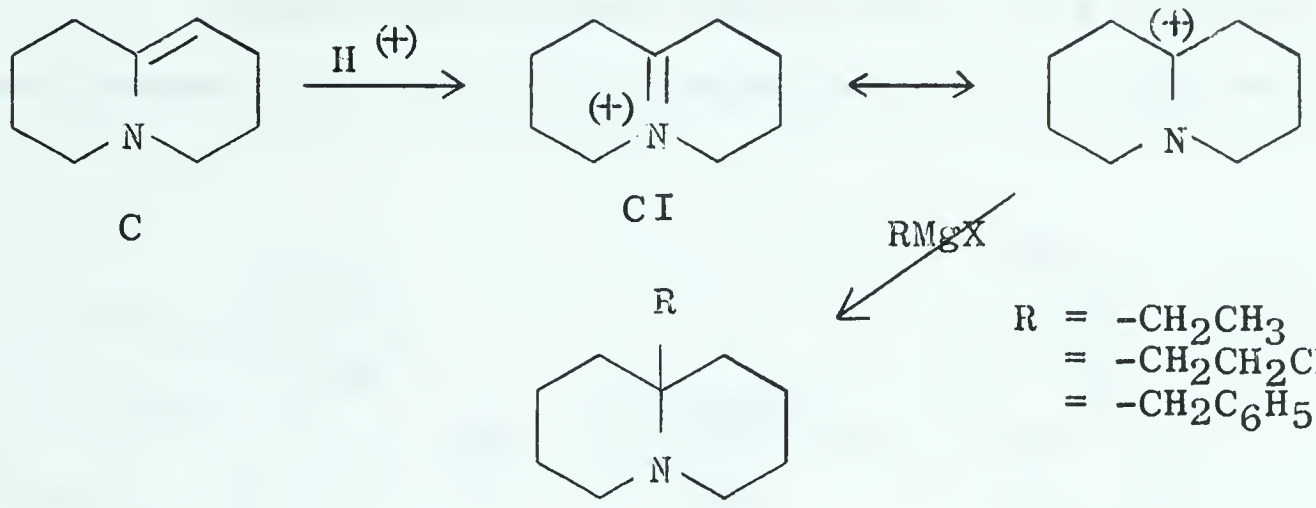
40-60% unreacted XXVIII. The explanation, of course, is that XXVIII perchlorate is much more soluble in the perchloric acid-ethylene glycol solution than is XCVIII. XXVIII could be recovered by basification of the filtrate from which XCVIII had been removed, and extraction with ether or petroleum ether. This method of "trans-derivatization" thus served not only to transform XXXVI to XCVIII, but, at the same time, and fortuitously, to separate unreacted XXVIII.

Since a route to XCVIII which provided it in good yield had been developed, attention was now directed to an investigation of the reaction of XCVIII with various nucleophilic reagents. A discussion of the stereochemistry of XCVIII is deferred until later.

3. The Grignard Reaction of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine XCVIII with Allyl Bromide and Methallyl Chloride

As is discussed in the previous section, the purpose underlying the preparation of XCVIII was to modify 9-methoxyjulolidine XXVIII in such a way that it would undergo easy reaction at carbon 11. Since XCVIII would be expected to react readily with nucleophilic reagents at this carbon atom, the most likely way to form a new carbon-carbon bond at carbon 11 appeared to be via reaction with an organo-metallic reagent. For example, Leonard (55) has prepared iminium salts CI of the enamine C and successfully treated these with various Grignard reagents, as shown in

equation 29. The Grignard reaction thus seemed to be well suited. The choice of an organic halide to form the



C CI (29)

Grignard reagent was governed by two criteria. These were: (a) the essential presence of a chain of three carbon atoms to enable the formation of the bridge, and (b) the equally essential presence of a functional group of some sort in the halide so that a centre would be available which could be used to close the ring at carbon 8 or 10 of XCVIII and so form the bridge-ring. Two halides which fulfil these requirements and which were readily available are 3-bromopropene, "allyl bromide" CII, and 3-chloro-2-methylpropene, "methallylchloride" CIII. The latter was preferred since

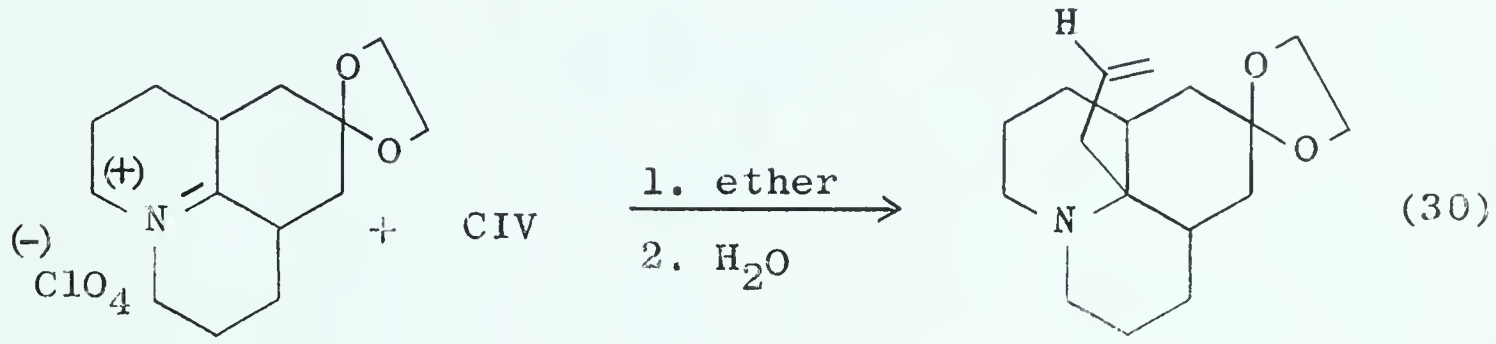
$CH_2 = CH-CH_2-Br$ CII

$CH_2 = \overset{CH_3}{\underset{|}{C}}-CH_2-Cl$ CIII

the 2-methyl group corresponds to the C-methyl group in the bridge-ring of lycopodine. The results using CII and CIII will be discussed separately.

(a) The Reaction of XCVIII with Allyl Magnesium Bromide

This reaction was carried out in a straight forward manner as indicated in equation 30. It had been found



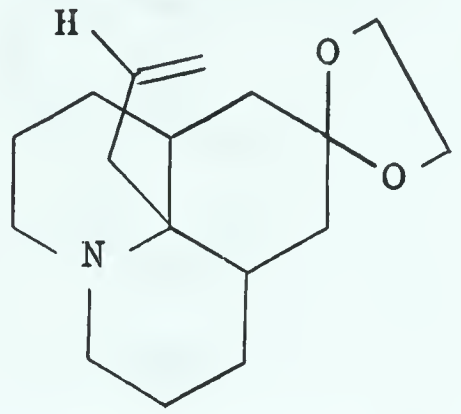
XCVIII CV (30)

(57) that allyl magnesium bromide CIV could be formed in the usual way, that is by reacting CII with magnesium metal in refluxing ether, in accord with equation 31. Addition

$$CH_2{=}CH\text{-}CH_2\text{-}Br + Mg \xrightarrow[\text{reflux}]{\text{ether}} CH_2 = CH\text{-}CH_2\text{-}MgBr \qquad (31)$$

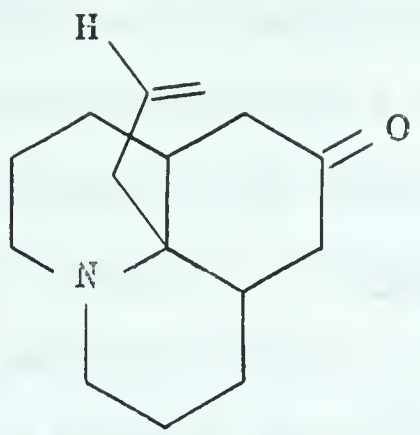
of powdered XCVIII to the refluxing solution of CIV gave after aqueous hydrolysis and the usual work-up an oil containing two components, as indicated by thin layer chromatography. One of these was unreacted XCIX. The infrared spectrum of the mixture in carbon tetrachloride displayed bands at 1650 cm^{-1} (enamine) and 3080, 1630 cm^{-1} (mono-substituted or unsym-disubstituted olefin), thereby indicating the likely presence of some 9-ethylenedioxy-

11-allyl-7a,8,9,10,10a,11-hexahydrojulolidine CV, the anticipated reaction product.



CV

Treatment of this mixture with perchloric acid and ethylene glycol as before yielded an insoluble salt, identified as starting material (XCVIII) by comparison of the infrared spectrum of the insoluble salt obtained above with that of authentic XCVIII. Basification of the perchloric acid ethylene glycol solution after removal of XCVIII and extraction with petroleum ether yielded an oil which again contained two components as indicated by thin layer chromatography, but this time neither was starting material. The infrared spectrum of this mixture displayed bands at 3079 cm^{-1} (olefin), 1714 cm^{-1} (medium intensity, carbonyl group), and 1632 cm^{-1} (weak, olefin). This spectrum could be explained by assuming the presence of both CV and the corresponding ketone CVI. This latter presumably could arise by hydrolysis of CV at some stage in the treatment with perchloric acid. Subjection of this new mixture to short path distillation in a collar flask at 110°C. and 0.1 mm did not effect a separation of the



CVI

components, nor did column chromatography on alumina. Since it thus appeared that the mixture of CV and CVI could not readily be separated by conventional means, an attempt was made to reconvert CVI to its ethylene ketal derivative CV by treatment of the mixture with ethylene glycol and para-toluenesulphonic acid in benzene solution at reflux temperatures. In this way the mixture could be "separated" by converting one of its components into the other. The reaction is indicated in equation 32. A high



CV

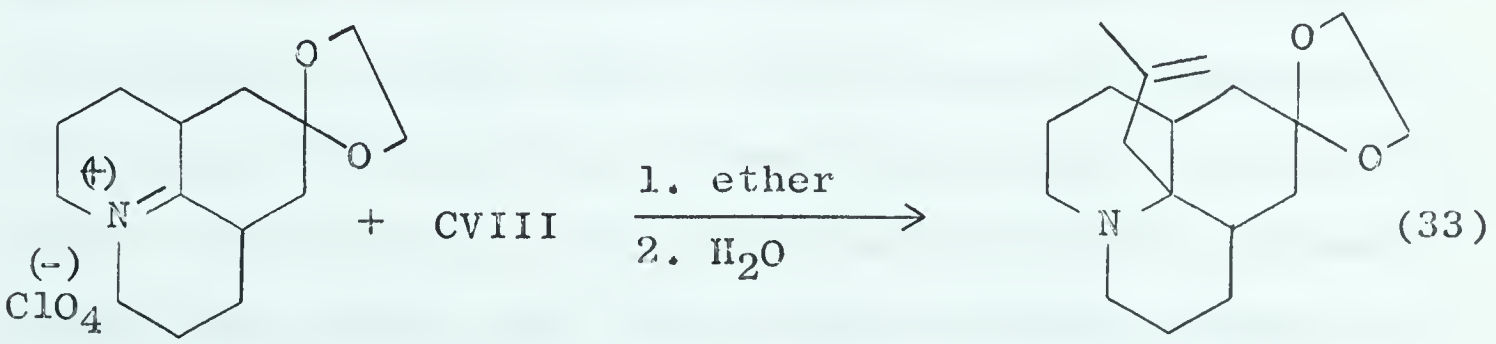
yield of a crystalline substance (m.p. 107°C.) was thus obtained. Thin layer chromatography indicated a single component. The infrared spectrum (Figure 4) of the

crystals displayed absorption at 3080 cm^{-1} (olefin), 2810, 2780, 2755, 2695, 2680 cm^{-1} (Bohlmann bands, see the Introduction and "Stereochemistry") and 1630 cm^{-1} (olefin). The n.m.r. spectrum (Figure 14) contained maxima at τ 9.0-7.4 (complex), τ 6.2 (singlet, -O-$\underline{CH_2}\underline{CH_2}$-O-), and τ 4.88 ($\underline{H_2}C{=}\overset{H}{\overset{|}{C}}$-). The mass spectrum (Figure 28) of this material, while not providing a peak at m/e 277 corresponding to the molecular ion, does support the structural assignment, as will be more fully discussed in the appropriate section. All this spectral data, as well as the mode of formation show that the crystalline material is pure CV.

This sequence of reactions provided CV in 40-50% yield from XCVIII, and while only a qualified success as a preparative method, seemed to be sufficiently promising to warrant investigation of the similar reaction of XCVIII with methallyl chloride CIII.

(b) The Reaction of XCVIII with Methallyl Magnesium Chloride

This reaction was carried out in a straight forward manner, as indicated in equation 33. The first attempt,



XCVIII CVIII

using diethyl ether as the reaction medium required some 60 hours to form the methallyl magnesium chloride CVII (equation 34) and seven additional days for reaction with XCVIII. However, there was obtained in this way an 89%

$$CH_2=\overset{CH_3}{\underset{|}{C}}-CH_2-Cl + Mg \xrightarrow[\text{reflux}]{\text{ether}} CH_2=\overset{CH_3}{\underset{|}{C}}-CH_2-MgCl \qquad (34)$$

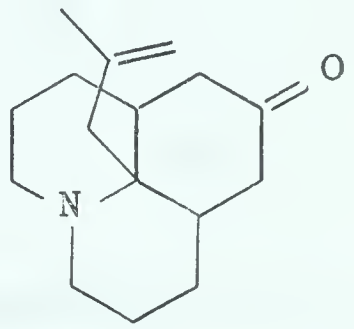
CIII CVII

yield of an oil whose infrared spectrum as determined in carbon tetrachloride displayed absorption at 3072, 1630, 888 cm^{-1} (unsym-disubstituted olefin). This oil readily formed a crystalline perchlorate whose infrared spectrum displayed bands at 3105 cm^{-1} ($-\overset{\oplus}{N}-H$), 1638 cm^{-1} (olefin), 1100 cm^{-1} (ClO_4^-). These spectral data, especially the band at 1630 cm^{-1} in the base and 1638 cm^{-1} in the salt, indicate loss of the enamine function of XCVIII, and its replacement by a disubstituted olefin. Thus the oil is in all likelihood CVIII.

In other work carried out in this laboratory it had been found (57) that the desired Grignard reagent, methallyl magnesium chloride, could be formed by reaction of methallyl chloride with a large excess of magnesium in refluxing tetrahydrofuran. The time required is only 12-16 hours. Incorporating this modification into the present scheme, and adding the finely powdered XCVIII directly to the refluxing tetrahydrofuran resulted in the production of 95% of an oil with the same spectral characteristics as

those of the oil obtained in the reaction using ether as solvent. The total reaction time was 13-18 hours. This procedure was employed regularly in all subsequent Grignard reactions.

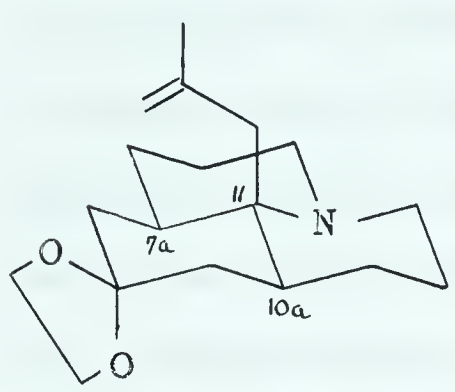
Returning now to the analysis of the oily reaction product, thin layer chromatography revealed the presence of two components in this oil, one major, the other minor, neither of which was starting material. Possible hydrolysis of the 9-ethylenedioxy group of CVIII to a 9-ketohexahydrojulolidine as shown in equation 35 giving rise to one of the

CVIII $\xrightarrow{H_2O}$  (35)

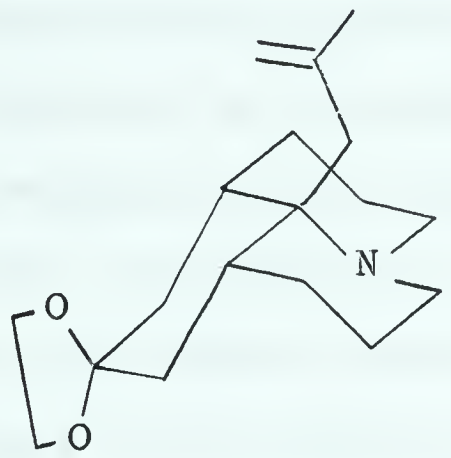
CIX

components could be ruled out since the infrared spectrum displayed only weak olefinic absorption in the region 1600-1750 cm^{-1} and no carbonyl absorption. The n.m.r. spectrum (Figure 15) of the oil displayed resonance at τ6.19 ($-O-CH_2-CH_2-O$) and τ5.24 (poorly resolved, doublet, splitting ca 5 cps, $-\underset{|}{C}=CH_2$). The relative integrated ratio of these bands was 2:1. If any appreciable CIX existed in the sample, this ratio would be expected to decrease, and so the presence of any large amount of CIX in the reaction product may again be ruled out. It is thus apparent that the components of

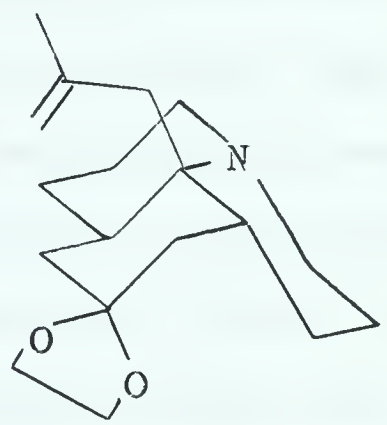
this oil are stereoisomers. As is discussed fully in the section on stereochemistry, there are three possible stereoisomeric hexahydrojulolidines, and hence three stereoisomeric possibilities for CVIII. These are CX (all trans), CXI (all cis), and CXII (trans-cis). The terms cis



CX



CXI



CXII

and trans refer to the relative configuration of the centres 7a, 11, and 10a in that order.

At this point the only evidence available to indicate the presence of a stereoisomeric mixture came from thin layer chromatography. Infrared measurements provided no clue, and the mixture was essentially transparent to ultra-violet radiation. The n.m.r. spectrum (Figure 15), determined as usual in carbon tetrachloride, similarly gave no sign. As mentioned above the olefinic resonance at τ5.24 was a poorly resolved doublet, and the ethylenedioxy band at τ6.19 a sharp singlet. It has frequently been observed that chemical shift values for a particular substance are often quite different when the spectrum is measured using an aromatic compound as the solvent, than

they are when the solvent is non-aromatic. These changes in the position of the chemical shift may be attributed to the anisotropy of the magnetic susceptibility of the aromatic solvent. The changes are often different for different compounds, and cases of accidental equivalence of the chemical shift of a proton or group of protons in two different substances may sometimes be detected by remeasuring the spectrum in an aromatic solvent. When the spectrum of the Grignard product was determined in benzene solution (Figure 16), the olefinic resonance had collapsed to a broad singlet and shifted downfield to τ 5.08. The resonance attributed to the ethylenedioxy protons was now present as two sharp singlets, shifted well upfield, at τ 6.37 and 6.40 . It should be pointed out that this shift can be explained in terms of the non-equivalence of the two methylenes of the ethylenedioxy group, but for reasons now to be presented, this explanation is not felt to be applicable.

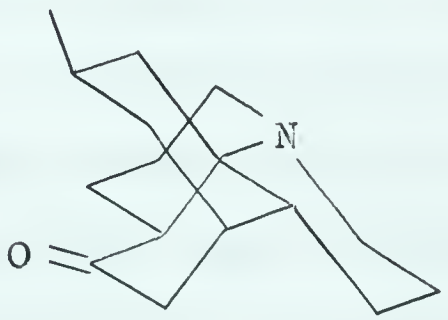
Attempts to separate the Grignard product mixture by short-path vacuum distillation were unsuccessful, as were attempts by conversion of the mixture to perchlorate derivatives, crystallization, and reconversion to the bases. Column chromatography of the oily bases on neutral alumina did, however, effect some purification. Initial fractions contained a mixture of the two components, which now appeared to be somewhat enriched in the minor component. It did not prove possible to isolate this component in pure form. Further elution yielded a low-melting (54-56^{o}C.)

crystalline solid, to the extent of about 40% of the weight of the original mixture. This solid gave only a single spot on thin layer chromatograms, corresponding in polarity to the major component of the original mixture. The n.m.r. spectrum (Figure 17) of the crystals, determined in benzene solution, showed resonance at τ 6.37 attributed to the ethylenedioxy protons with now only a small shoulder at τ 6.40. Rechromatography of the solid failed to produce any material with spectral characteristics different than the solid. We conclude that the shoulder at τ 6.40 is probably due to some non-equivalence of the ethylenedioxy protons in the major component, but that the peak at τ 6.40 in the mixture is due to the first component.

It is now appropriate to deal more fully with stereochemistry and the determination of relative configuration of the compounds discussed to this point.

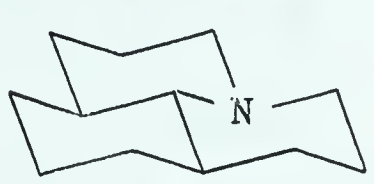
4. Stereochemistry

Stereochemical considerations are of importance in any projected synthetic sequence leading to lycopodine (I)

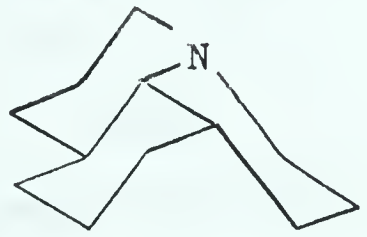


I

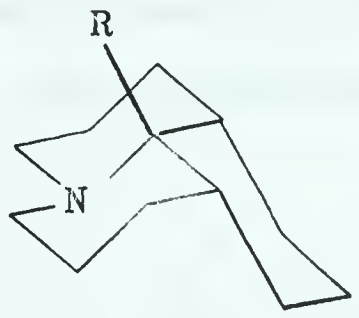
since the hexahydrojulolidine system from which it is derived and through which the present work aims can assume three conformations XL, XLII (R=H), XLI. As can be readily



XL



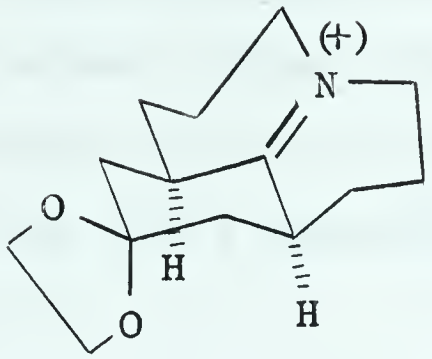
XLI



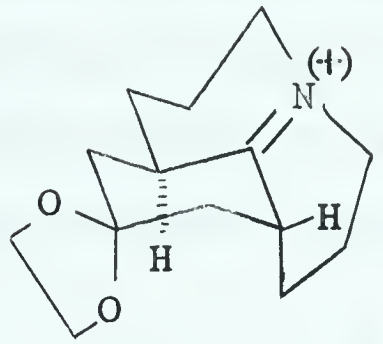
R { allyl
methallyl
-CN
-H

XLII

seen, lycopodine I is derived from the trans-cis hexahydrojulolidine XLI. It should first be noted that XCVIII can exist in two stereoisomeric forms CXIII (cis) and CXIV (trans). If the formation of the salt XCVIII from the enamine XXXVI is thermodynamically controlled, CXIII would be the expected product, whereas a kinetically controlled salt formation could lead to either. The determination of the stereochemistry of the products of the Grignard reactions will serve to determine the stereochemistry of the salt.

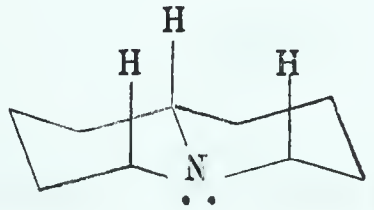


CXIII

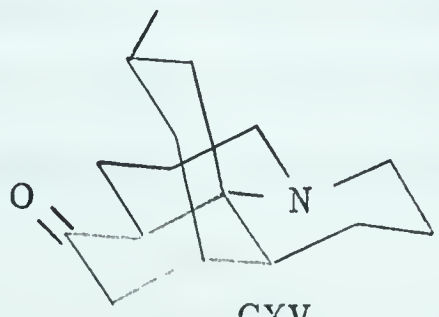


CXIV

As has already been discussed, Bohlmann (25) has indicated that the presence of the following part structure, with at least two carbon-hydrogen bonds oriented 1,2-trans-

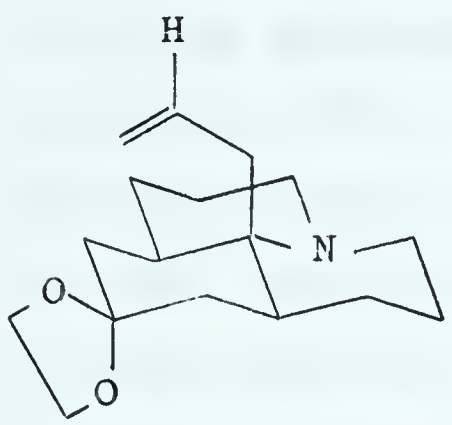


diaxially to the unshared pair of the nitrogen, may be detected in a quinolizidine molecule by the appearance of a series of three to six bands in the region 2900-2600 cm^{-1} of its infrared spectrum. These are the so-called "Bohlmann bands." The infrared spectra of both XL and XLII (R=H) display (25) such bands, while XLI does not, nor does lycopodine I or any of the related family of alkaloids of known stereochemistry. As has been discussed, acrifoline III and epi-lycopodine CXV do show these bands (10).

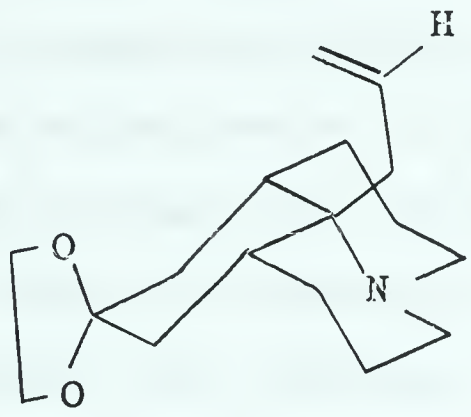


CXV

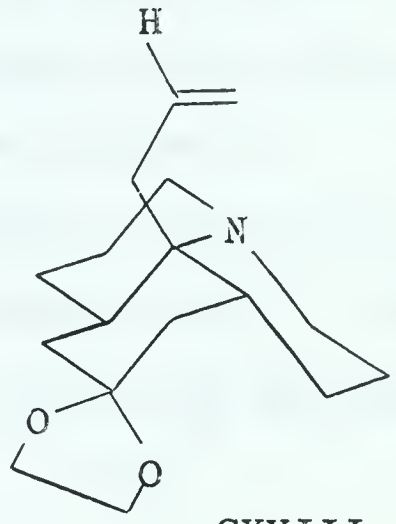
The presence of well defined Bohlmann bands in the infrared spectrum of CV coupled with the fact that only one product arises from the reaction in which it is produced indicates that its relative configuration can be either CXVI or CXVII since both of these would be expected to



CXVI



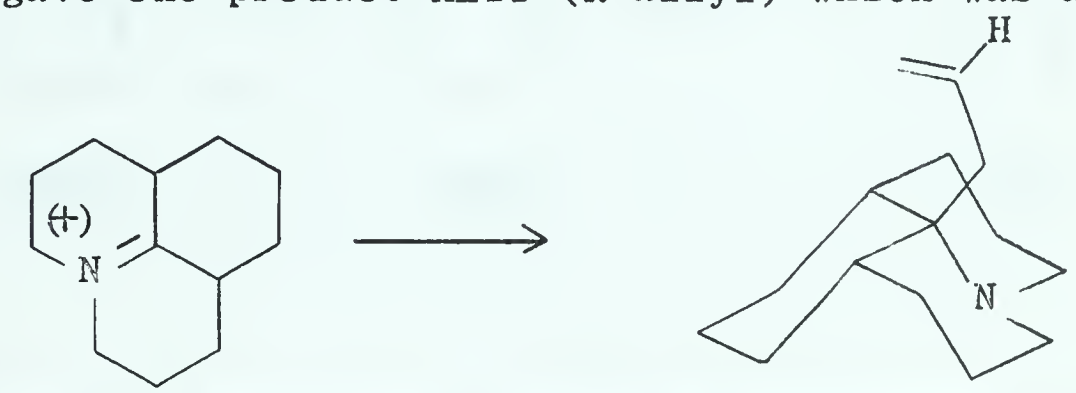
CXVII



CXVIII

exhibit Bohlmann bands. The third conformation CXVIII can be ruled out since it would not show these bands in its infrared spectrum. A choice of one of the remaining two as the correct representation can be made on the bases both of steric considerations and analogy. If we consider the two forms of the iminium perchlorate CXIII and CXIV from which this adduct forms, it must be that if only one product is obtained, then only one of these forms can react. If CXIV reacts, it will lead to CXVIII, which has been already eliminated as a possibility. If CXIII reacts, it can lead to either CXVI or CXVII. It thus becomes a question of deciding at what side of the molecule CXIII the allyl magnesium bromide CIV will attack. The answer to this question lies in the steric environment of C-11 of CXIII. The carbon atoms 7a, 11, and 10a of this salt must lie in

a common plane. The carbon atoms 8 and 10 each with their two attached hydrogen atoms will be situated above this plane, while the two hydrogen atoms attached to C-7a and C-10a (one each) will lie below the same plane. It is apparent that the methylene groups will be sterically more hindering than will the hydrogen atoms, and hence attack of CIV is predicted to occur from the α side of the molecule, producing CXVII. The second basis for the choice of structure CXVII is by analogy with the same reaction carried out (57) using the 9-deoxy tetrahydrojulolidine CXIX. This reaction gave one product XLII (R=allyl) which was assigned

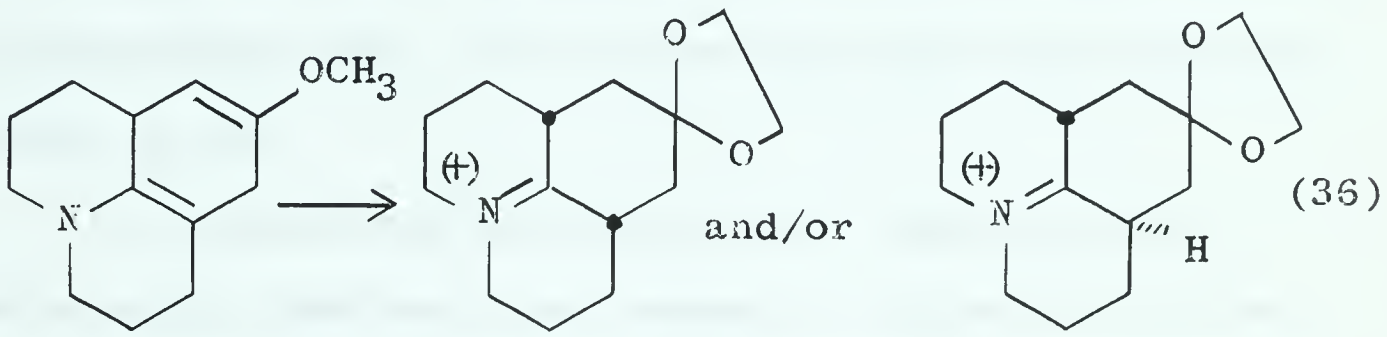


CXIX XLII (R=allyl)

the all cis configuration. Since the present reaction is closely parallel to the reaction CXIX $\longrightarrow$ XLII (R=allyl), it is expected that similar products will result. On these two grounds then, configuration CXVII is tentatively assigned to the material obtained using XCVIII.

The case of the Grignard reaction of XCVIII with methallyl chloride is somewhat more complex in that a two component reaction product is obtained. Here the crude product displays clearly Bohlmann bands. There are thus two sets of conformational possibilities to be considered.

These are: (a) one component is either CX or CXI, the other being CXII, or (b) one component is either CX or CXI, the other being either CXI or CX. A decision can be made between these two by a further consideration of the reactions of the two stereoisomeric salts CXIII and CXIV with methallyl magnesium bromide CVII. Equation 36 illustrates the formation of the two salts (compare with



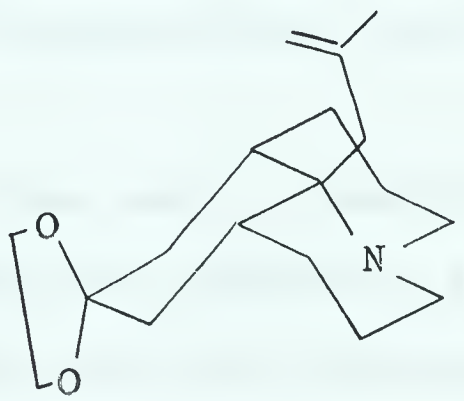
(36)

XXXVI CXIII CXIV

equation 28). A Grignard reaction is now carried out on this (these) perchlorate (s). There are three possibilities to be considered here: (a) the product of equation 36 is CXIII only, (b) it is CXIV only, and (c) it is both CXIII and CXIV. Taking possibility (a) first, reaction of CXIII with methallyl magnesium chloride could proceed with attack from the α and the β sides of the molecule, to produce a mixture of CX and CXI since neither direction of approach can be said to be absolutely blocked. Considering possibility (b), if the product of equation 36 is CXIV only, then the Grignard reaction can only yield CXII. Finally, possibility (c) predicts that the Grignard reaction mixture would be expected to contain three components. Experimentally

it is found that this reaction product contains two components only, displaying Bohlmann bands. It thus can be said with assurance that the mixture is one containing CX and CXI. A portion of the major component of this mixture is separable via column chromatography, and is assigned structure CXI by analogy with the reaction of CXVIII with allyl magnesium bromide, and by detailed steric consideration of the reaction with the perchlorate CXIII to which reference has already been made. The second component must thus by exclusion be CX.

The behaviour of this mixture during column chromatography deserves some comment. Inspection of the structures CX and CXI indicates that CXI is expected to be a much more hindered base than is CX. This is due to the



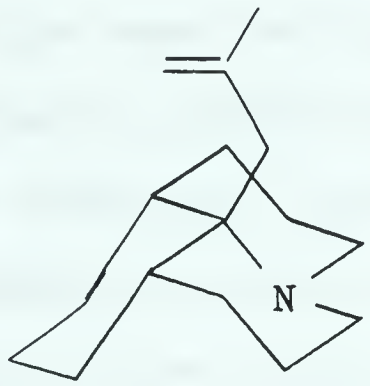
CXI

large steric effects which will be exerted by the two axial methylene groups at carbon 7a and 10a, disposed in a 1,3-diaxial relationship to the unshared pair of electrons on the nitrogen, causing much interference with reactions involving these electrons, and hence interfering with reactions of the nitrogen in CXI relative to CX which has none of these interactions. Predicting the behaviour of

these two during chromatography, CX is expected to be the more strongly adsorbed of the two since it is the less hindered base, and hence the last to elute, or in other words to be the more polar. This assertion finds support in the work of Bohlmann, (25) already cited, who reports that column chromatography of mixtures of XL, XLII (R=H) and XLI, result in the elution first of XLII (R=H), the most greatly hindered base of the three, followed by XL and then XLI. Here it is apparent that polarity parallels the degree of steric hindrance of the nitrogen. What is actually observed in the present work however is that the reverse is true. CXI is the more polar of the two, and is thus eluted last. In this case the more hindered is the more polar, and the less hindered is the less polar. It is possible that the ketal function is controlling the adsorption behaviour in our case.

An attempt was made to demonstrate the stereochemistry of the separable component of the Grignard reaction product of XCVIII with methallyl chloride by taking advantage of the method used by Bohlmann (58) in the case of the isomeric hexahydrojulolidines. This worker found that under certain specified conditions both XL and XLI would react with methyl iodide to form the corresponding methiodide derivatives, but that under these same conditions XLII (R=H) would not, thus providing a criterion for distinguishing between XLII (R=H) and XL or XLI. The procedure clearly owes its success to the fact that XLII (R=H) is a much more hindered base than either of the other two. In the present

work this method was to be applied in the following way. Parallel reactions of the single component and the closely related 11-methallylhexahydrojulolidine XLII (R=methallyl) with methyl iodide were to be made in solvents of gradually



XLII (R=methallyl)

increasing polarity, until one or the other or both formed a methiodide derivative. If the single component reacts in a solvent in which XLII (R=methallyl) does not, then the former is a less hindered base than XLII (R=methallyl) and its structure may thus be represented by CX. If conditions cannot be found wherein preferential reaction of one of the substances occurs, it is likely that the single component and XLII (R=methallyl) have the same configuration (CXI). In the unlikely case of XLII (R=methallyl) reacting when the single component does not, then the latter is the more hindered of the two, and undoubtedly has the conformation represented by CXI.

This reaction was carried out in solvents ranging in polarity from anhydrous ether to a solution of 20% methanol and 80% ether. It was found that methiodide formation of both substances occurred in the latter solvent, but not in one consisting of 15% methanol and 85% ether.

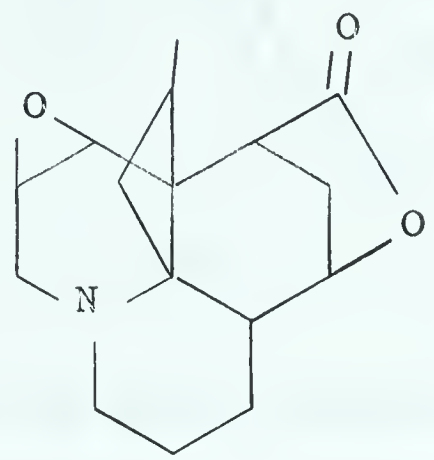
Repetition of the reaction in 17% methanol and 83% ether yielded mixtures of unreacted base and methiodide of both substances. It would thus appear that the two materials are very alike in the steric environment of the nitrogen and thus likely have the same configuration. This is in agreement with conclusions already drawn.

It must be noted that stereoisomer CXI is not ideally suited to undergo a reaction involving carbons 8 or 10 and a modified form of the carbon 11 methallyl chain since in CXI the C-11 chain is equatorially arranged with respect to the B ring, and it must be axially oriented to undergo ring closure. The isomer CX is better arranged for this type of reaction, but its presence in such small amounts and our inability to isolate it in pure form were not encouraging. In most of the work to be discussed subsequently, the crude reaction mixture containing both components is used. In some few cases, the pure isomer CXI is used, and these will be clearly indicated.

5. The Preparation of 9-Ethylenedioxy-11-(2-ketopropyl)-7a,8,9,10,10a,11-hexahydrojulolidine perchlorate CXXIII and Attempts at its Photochemical Conversion

The production of relatively large amounts of the all-cis isomer CXI caused a certain amount of re-evaluation of the objectives of the overall researches. This isomer is not readily adaptable to the lycopodine synthesis as it was at this point visualized. There is however another member of the Lycopodium alkaloids, annotinine II, in which

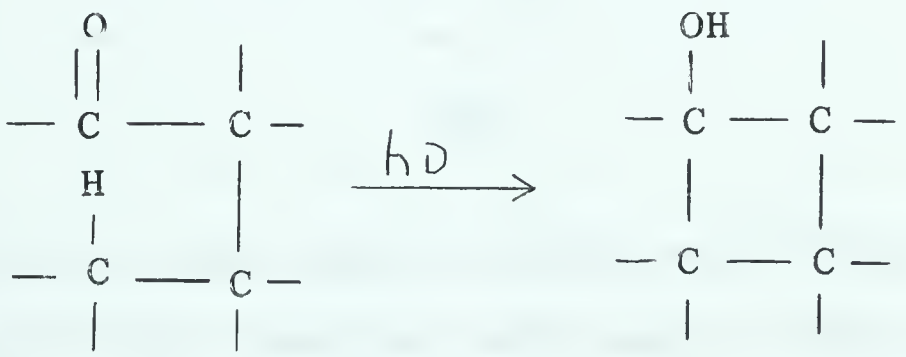
the bridge-ring is now four membered, with points of attachment at carbons 10a and 11. It was felt desirable to investigate the possibility of using CXI as a means of



II

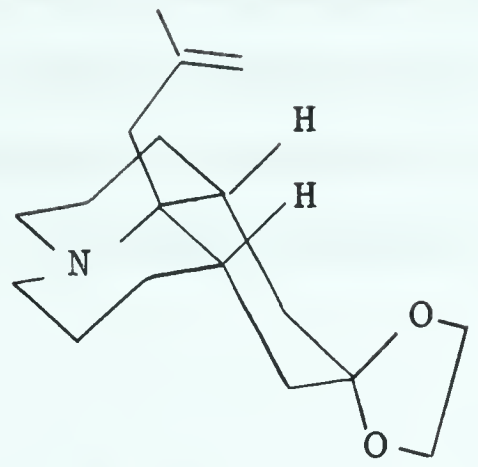
forming such a bridge.

As is discussed previously, the Yang reaction provides a method of forming cyclobutanols by photochemical conversion of suitable ketones. The reaction occurs between the carbonyl group and a carbon-hydrogen bond of the γ-carbon, as indicated in equation 37. This reaction should



(37)

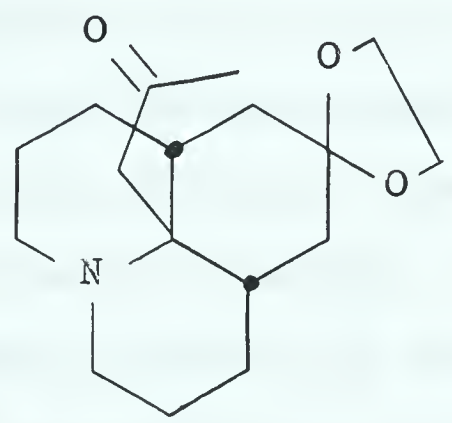
be especially favourable in a situation where the γ-carbon is rigidly held close to the carbonyl group. Such a circumstance would seem to pertain in structure CXI. Were the exo-methylene of CXI converted to a carbonyl group, then the two carbon-hydrogen bonds of carbons 7a and 10a should



CXI

be ideally disposed for such a closure as is shown in equation 37.

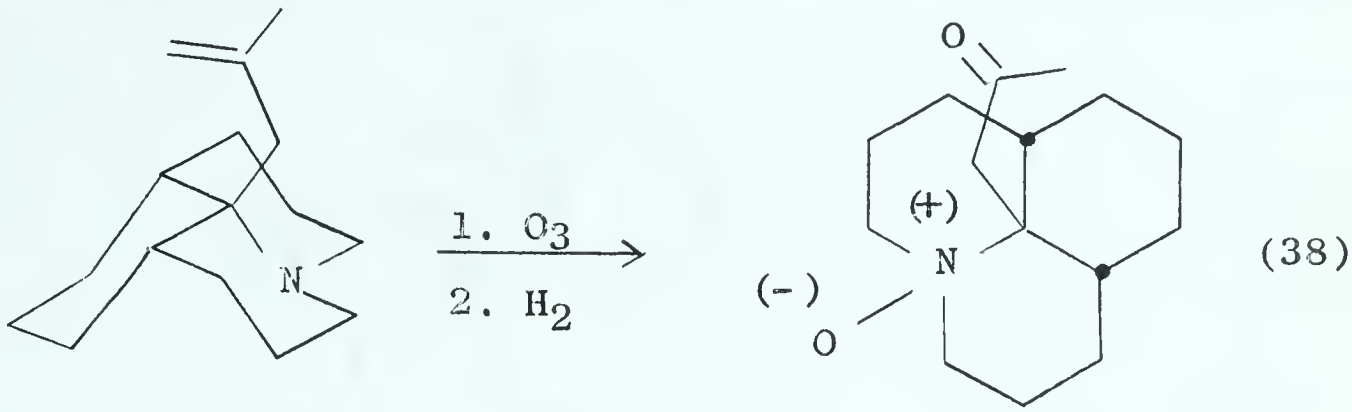
The first step of course is the generation of the ketone CXX. The solid circles conventionally indicate β hydrogen atoms. First attempts at this reaction were



CXX

carried out on the closely related model XLII (R=methallyl). Treatment of this compound with ozone at Dry-Ice temperatures followed by reduction of the unisolated ozonide with hydrogen over $PdCO_3$/charcoal yielded an almost quantitative yield of an oil, whose infrared spectrum in chloroform displayed bands at 3400, 1700, 1650 cm^{-1}. There was no evidence of Bohlmann bands. It thus appeared that as well as removing the exo-methylene group, the ozonation

had formed an amine oxide derivative CXXI, as indicated in equation 38. Horner (59) reports that the oxides of tertiary amines may conveniently be prepared by allowing them to react with ozone at -50°C. Various attempts to reduce the N-oxide



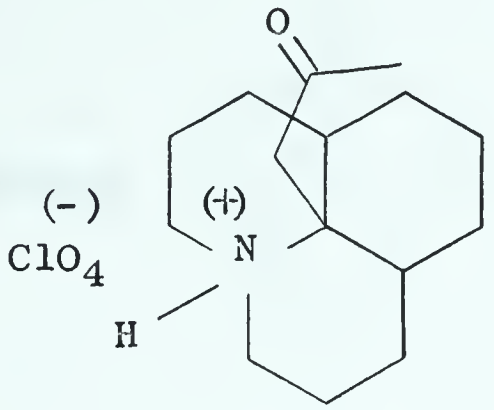
(38)

XLII (R=methallyl) CXXI

(using Adam's catalyst, zinc/acetic acid, zinc/sodium hydroxide, zinc/anhydrous acetic acid) failed to produce any material which displayed Bohlmann bands, or whose infrared spectrum was appreciably different from that of CXXI. Despite the unwanted oxide formation, it was nevertheless apparent that by this procedure the carbon 11 methallyl chain could readily be modified to the desired 2-ketopropyl chain. It was also apparent that protection for the basic nitrogen would have to be provided. Perhaps the most obvious protection was available by means of salt formation.

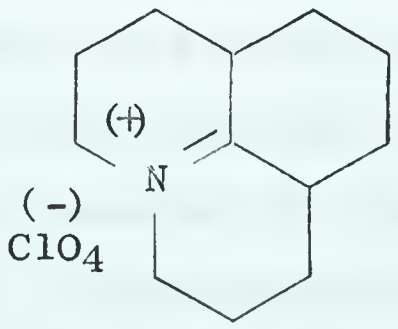
A further ozonation was carried out on this model compound XLII (R=methallyl) as its perchlorate derivative, followed by catalytic reduction of the unisolated ozonide at a hydrogen gas pressure of 30 psi. The reduction product obtained in 75% yield was identified as the ketone CXXII (m.p. 183-184° dec.) by the appearance in its infrared

spectrum (Figure 5) of a strong band at 1700 cm^{-1}, the disappearance of the olefinic absorption at 1632 cm^{-1}, and the retention of the peak at 1050 cm^{-1} associated with the perchlorate ion. It was apparent that perchlorate formation



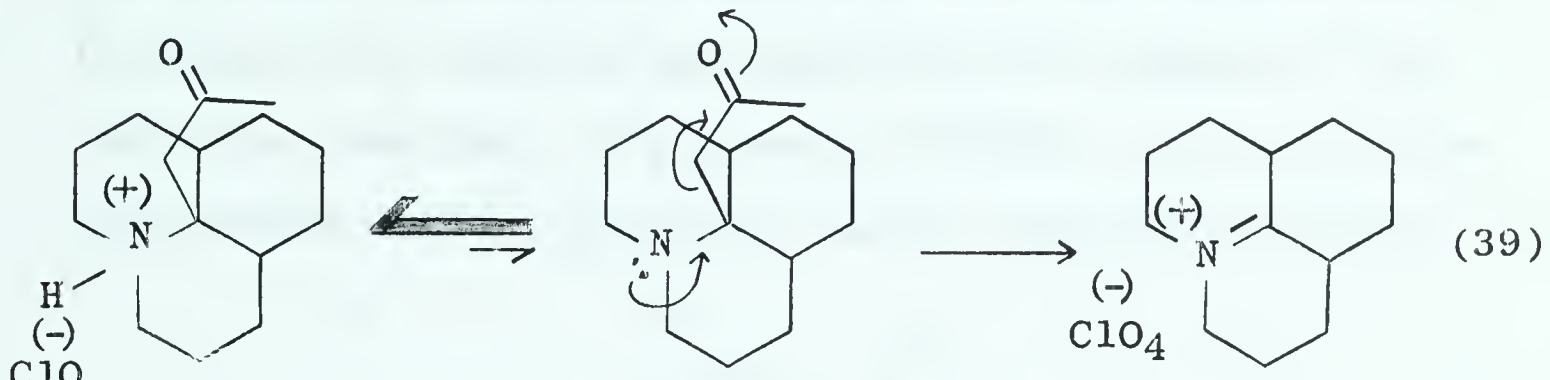
CXXII

was sufficient, as expected, to protect the nitrogen against undesirable oxidation, which had been experienced with the corresponding free base XLII (R=methallyl). The ketone CXXII was recrystallized from ethanol to yield a mass of shining white needles (m.p. 206-207°C.) whose infrared spectrum was markedly different from that of CXXII, in that the strong band at 1700 cm^{-1}, associated with the ketone, had disappeared, to be replaced by a band at 1665 cm^{-1} of medium intensity. Perchlorate ion absorption appeared at 1080 cm^{-1}. Comparison of this spectrum with that of authentic tetrahydrojulolidine perchlorate CXIX suggested the structure of



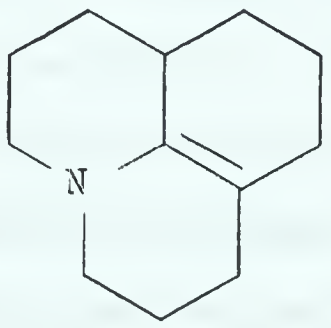
CXIX

the recrystallized material, which was confirmed as CXIX by mmp. determinations. This surprising retrograde Mannich reaction may be rationalized as shown in equation 39.



CXXII CXIX (39)

Treatment of CXIX produced by this reaction with aqueous sodium carbonate produced a high yield of an oil whose infrared spectrum displayed a band at 1630 cm^{-1} and was very similar to that of authentic enamine XXXVII. The oil, thus

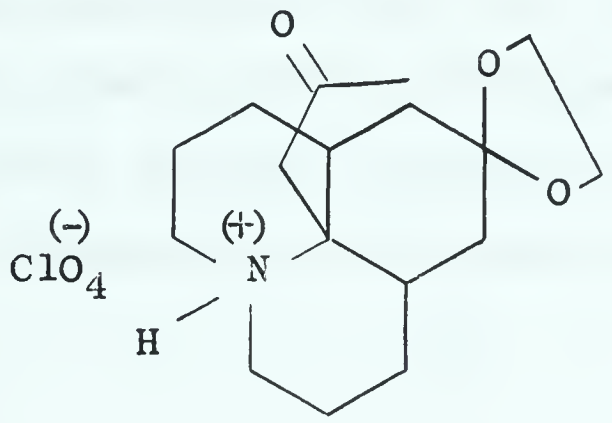


XXXVII

identified as XXXVII was reconverted to its perchlorate derivative, which was identical with the perchlorate CXIX obtained above as revealed by comparison of the appropriate infrared spectra. This decomposition (equation 39) foreshadowed serious difficulties to be experienced with the

main series of compounds.

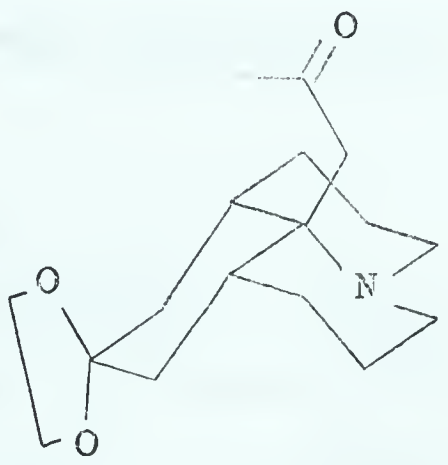
Returning to the direct line of synthesis, an ozonation was performed on the isomeric mixture of CX and CXI as their perchlorates again at Dry-Ice temperatures. As before, the ozonide was catalytically reduced. The reduction provided, in yields of 30-50%, the crystalline perchlorate CXXIII, insoluble in the reduction medium.



CXXIII

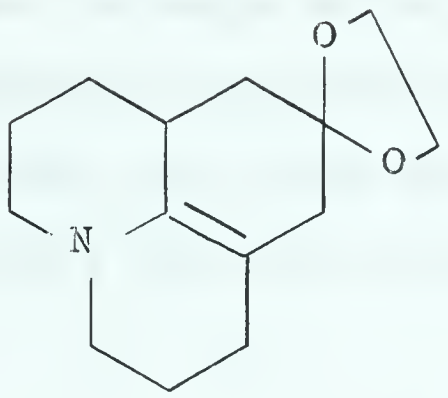
The substance displayed infrared bands (Figure 6) at 3120 cm^{-1} ($\overset{(+)}{-N-H}$), 1695 cm^{-1} (keto-carbonyl), 1405 cm^{-1} ($-CH_2-\overset{O}{\overset{\|}{C}}-$) and 1075 cm^{-1} ($\overset{(-)}{ClO_4}$), in good agreement with what would be expected from CXXIII. Treatment of the liquors freed of CXXIII by dilution with ether and filtration, with 1,3-diketo-5,5-dimethylcyclohexane (dimedone) yielded an amount of the dimedone derivative of formaldehyde, identified by m.p., m.m.p., and comparison with the infrared spectrum of the authentic derivative. The formaldehyde is formed by the cleavage of the methallyl group of CVIII as expected to give CXXIII. The infrared spectrum of the main ozonation product, and the isolation of formaldehyde from the reaction, provide convincing evidence in favour of structure CXXIII as the correct representation of the main ozonation product.

Basification of CXXIII with saturated aqueous sodium carbonate yielded an oil whose infrared spectrum displayed absorption at 1642 cm^{-1}. In addition, the n.m.r. spectrum showed bands at τ 8.23 (broad, complex), τ 7.25 (broad), τ 6.15. Neither of these physical measurements are in accord with what should be produced by the base CXXIV corresponding to CXXIII. The absence of carbonyl absorption in the infrared spectrum of this oil together with the appearance of a band at 1642 cm^{-1} suggested possible formation of an enamine by a reaction analogous to that shown in equation 39. Preparation of the perchlorate derivative of



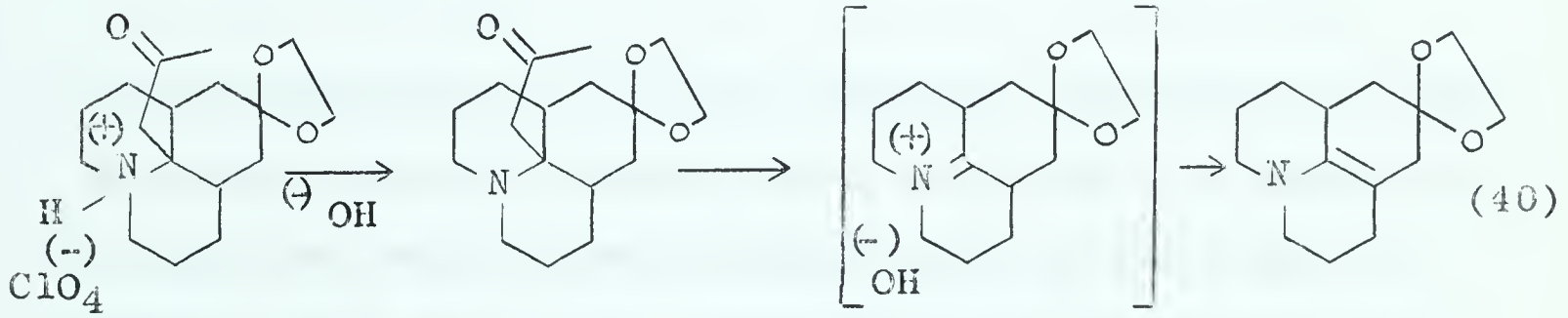
CXXIV

this oil gave a white crystalline substance, in whose infrared spectrum a band occurred at 1670 cm^{-1}, confirming the presence of an enamine in the base. Comparison of infrared and n.m.r. spectra revealed this carbonyl-free enamine to be in fact XCIX. It will be recalled that this compound is the free base corresponding to the iminium perchlorate XCVIII used in the Grignard reactions (see section 3), and thus represents somewhat of a movement backward in the synthetic scheme. The loss of the 2-ketopropyl group can be rationalized as shown in equation 40.



XCIX

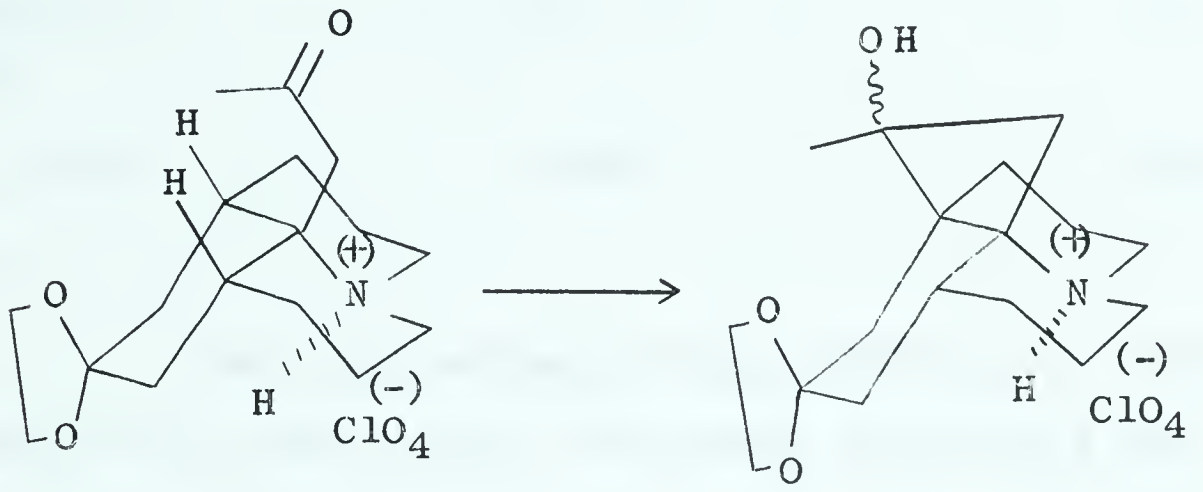
An attempt was made to produce CXXIV in the presence of an immiscible solvent (ether) in the hope that it could be extracted from the basic solution before decomposition occurred. An oil was obtained which was clearly a mixture



CXXIII CXXIV XCIX (40)

of ketones, displaying infrared absorption at 1700, 1690 and 1640 cm^{-1}. The band at 1700 cm^{-1} probably indicates some hydrolysis of the 9-ethylenedioxy group, and of course the enamine band at 1640 cm^{-1} indicates loss of the 2-keto-propyl chain to some extent. We were unable to isolate the base corresponding to CXXIV, apparently because of the facile reverse Mannich to give acetone and enamine XCIX (equation 40).

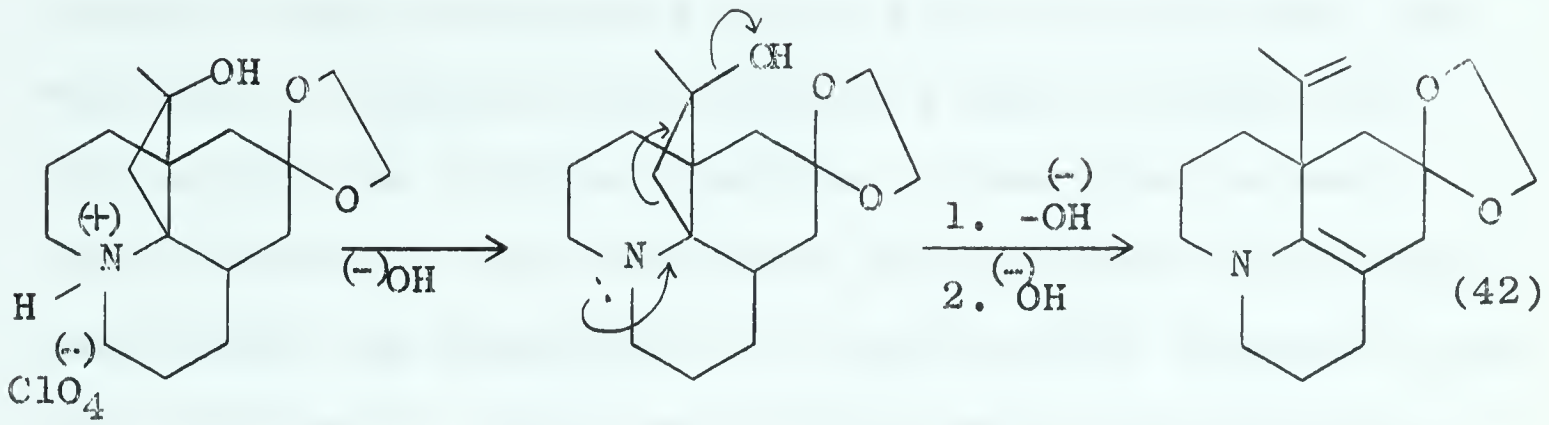
The necessity of retaining the amine salt imposed large restrictions on the media which could be used to carry out the photochemical Yang reaction. It was hoped that this reaction would take the course shown in equation 41 to produce the cyclobutanol derivative CXXV. It was not



CXXIII CXXV (41)

anticipated that difficulties would be experienced through the occurrence of a reverse Mannich reaction on formation of the free base corresponding to CXXV as had been with CXXIII, since it is more difficult to rupture the carbon-oxygen single bond than it is to polarize the π bond of a carbonyl group. If such a reaction did occur with CXXV, it would be expected to take the course shown in equation 42, and thus be readily recognizable since CXXVII contains both an enamine and an isolated double bond. The presence of the enamine function in CXXVII could be detected by the presence of a band at about 1650 cm^{-1} in the infrared spectrum of the base, which shifts to near 1680 cm^{-1} on formation of an amine salt. The exo-methylene would be readily observed by measurement of the n.m.r. spectrum of

the base.



CXXV CXXVI CXXVII

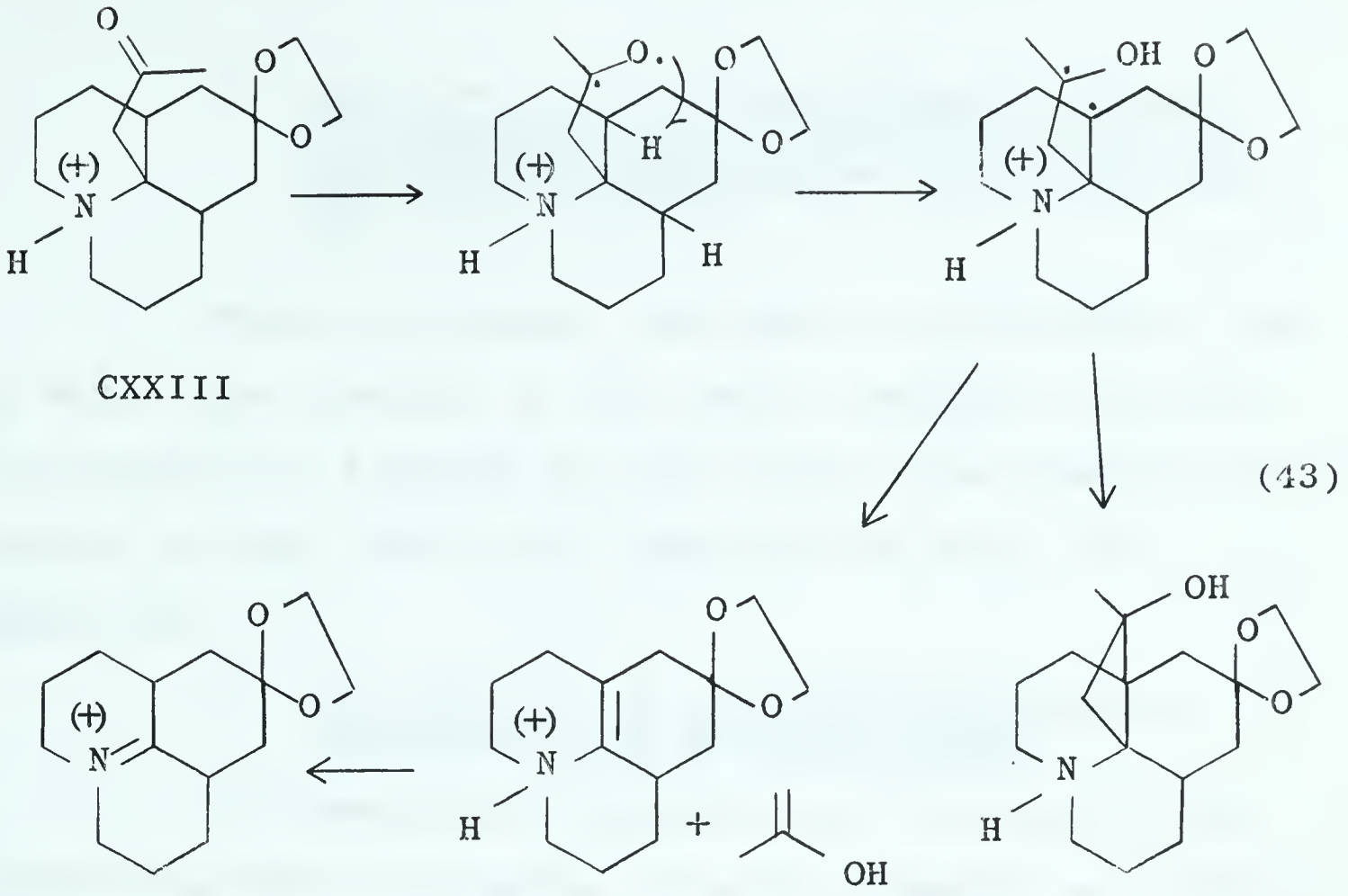
The first attempted Yang reaction of CXXIII was carried out using water, from which oxygen had been removed by prolonged boiling, as the solvent at a temperature of 75°C, for 6 hours. Basification of the yellow aqueous solution and extraction with chloroform gave a yellow oil. The infrared spectrum of this material and the corresponding perchlorate revealed it to be enamine XCIX. There was no trace of hydroxylic absorption in either of these spectra. It is of course not possible to say whether the loss of the 2-ketopropyl chain was photochemically induced, or did not occur until the basification during work-up.

Further photolyses were carried out using 1,2-dimethoxyethane as the solvent. These experiments yielded material whose n.m.r. spectrum could only be interpreted by postulation of the incorporation of solvent. These products were not investigated further.

Another solvent, photochemically less reactive than dimethoxyethane, in which CXXIII is soluble is

acetonitrile. Correspondingly, a reaction was carried out using this material as the solvent. The reaction was conducted at room temperature over a period of 48 hours, and monitored at intervals by removing a small aliquot and determining its infrared spectrum. These spectra were characterized by the progressive disappearance of carbonyl absorption, and appearance of a broad medium intensity band about 1670 cm^{-1}. There was no absorption attributable to hydrogen attached to positive nitrogen, although the typical strong band at 1080 cm^{-1} due to the perchlorate ion was present. Work-up of the reaction after 48 hours gave a quantity of brown crystals, identified by comparison of infrared spectra as XCVIII. No material was obtained which displayed any hydroxylic absorption. It thus was apparent that the reverse Mannich reaction had taken place, resulting in the expulsion of the 2-ketopropyl group. It is unlikely that this reaction proceeds via the mechanism shown in equation 40, since a basic nitrogen would be required. It is possible however to rationalize the cleavage of the chain by a mechanism involving the same intermediate as is required to effect the desired ring closure. This is outlined in equation 43, and is an example of the well-known photochemical "β-cleavage" of a ketone, another example of which has previously been discussed.

This cleavage reaction apparently proceeds much more readily than the ring closure, since no trace of the alcohol could be detected. As a result, attention was now returned to the modification of the methallyl chain of

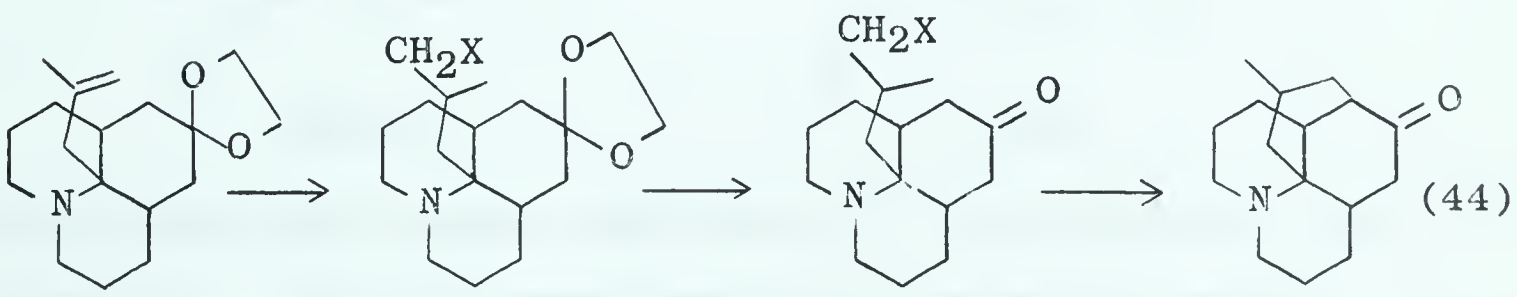


CXXIII

(43)

XCVIII CXXV

CVIII (the mixture of CX and CXI) to produce a suitable leaving group which could be expelled by a carbanion at carbon 8 or 10 as indicated in equation 44. It was felt



CVIII

(44)

that such a closure would be likely to occur with the all trans compound CX in the mixture. Another opportunity to

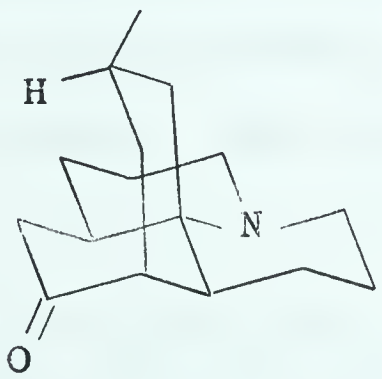
separate the mixture would occur at the tetracyclic stage.

6. Reactions Involving the Ethylenic Linkage of 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CVIII other than Formation of CXXIII.

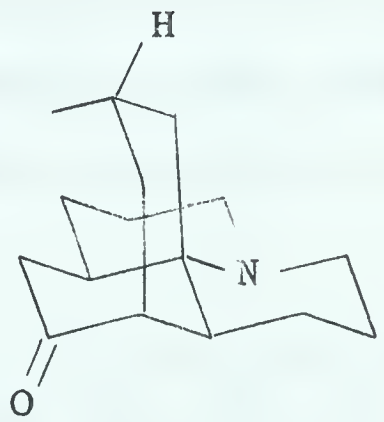
There are several reactions to be discussed, none of which lead directly to the type of reaction visualized in equation 44, although one does contain the possibility of leading in that direction. These will be dealt with separately.

(a) The Reaction of 11-Methallylhexahydrojulolidine with Molecular Oxygen

An unavoidable concomitant of the type of ring closure depicted in equation 44 is the committal to a definite stereochemistry of the bridge-ring methyl group as either of the epimers CXXVIII or CXIX, or a mixture of both. Structure



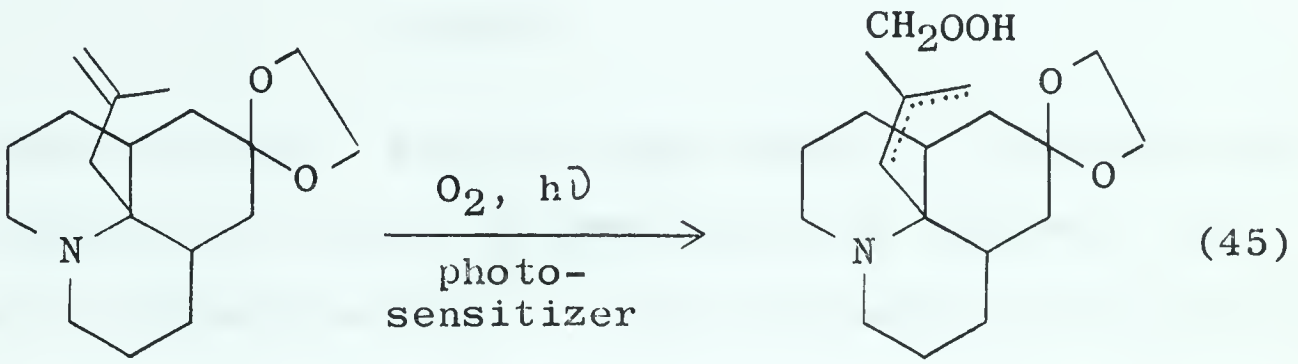
CXXVIII



CXXIX

CXXVIII has the bridge-ring methyl in the lycopodine conformation. Thus the development of a method to retain unsaturation at the same time as the closure occurred was felt to be desirable since then a specific reaction could be devoted to the stereochemistry.

The formation of an allylic hydroperoxide by the photosensitized reaction of an olefin with molecular oxygen appeared appropriate for this purpose (see Introduction). The reaction in this instance was visualized as shown in equation 45, with uncertainty in the position of the double

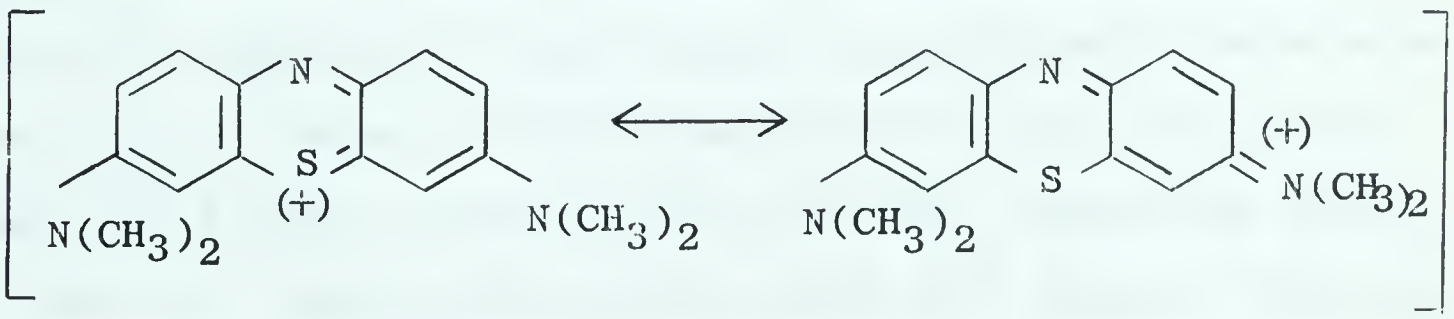


(45)

CVIII CXXX

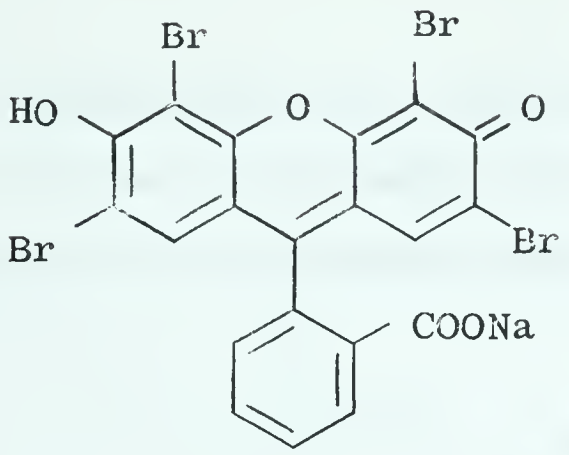
bond of the hydroperoxide CXXX being indicated by a broken line.

Choice of the photosensitizing agent was somewhat limited through the immediate availability of only two dyes thought to be suitable, methylene blue CXXXI and eosin yellow CXXXII. The first reaction carried out on CVIII used



CXXXI

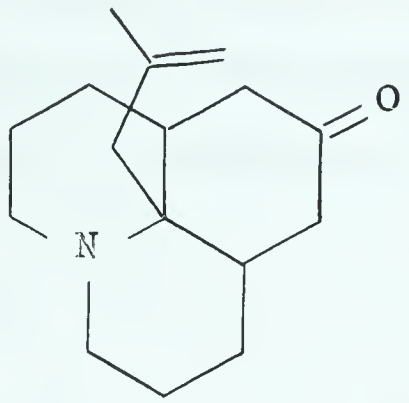
eosin yellow as the photosensitizer and ethanol as the solvent. The solution was irradiated in a pyrex tube by an ordinary mercury arc lamp while a stream of oxygen gas



CXXXII

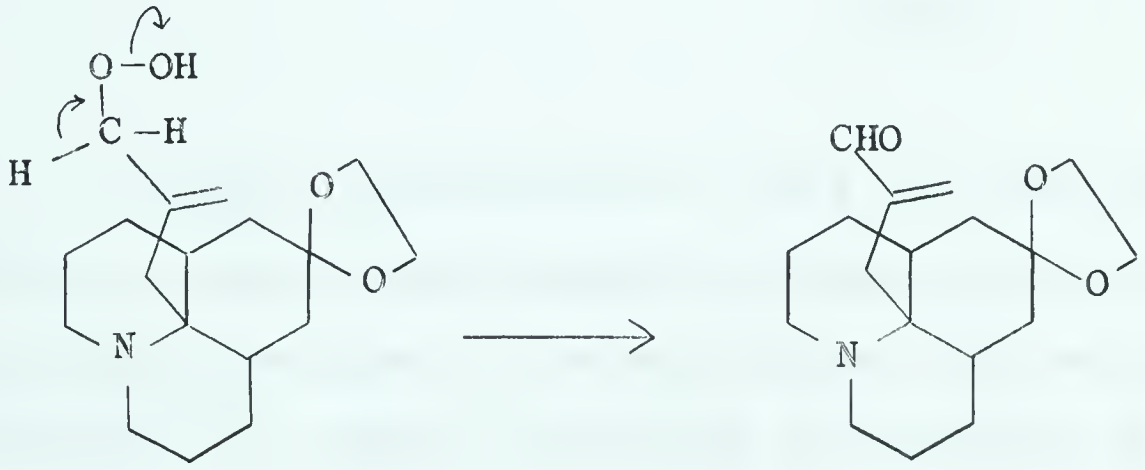
was passed through. Aliquots were taken at intervals and, after removal of the dye by adsorption on charcoal, subjected to infrared analysis. After 72 hours, only starting material was present, as indicated by thin layer chromatography, and an infrared spectrum indistinguishable from that of CVIII. The only thing which appeared to have occurred was extensive decolorization of the dye. Somewhat more success attended the second attempt, carried out using methylene blue instead of eosin yellow as previously employed. Other reaction conditions were essentially unchanged. The first aliquot, removed after 17 hours provided an infrared spectrum which displayed absorption at 3530 cm^{-1} (weak and broad), 3080 cm^{-1} (weak), 1700 cm^{-1} (medium), 1640 and 1630 cm^{-1} (doublet of equal intensity, and about the same as the 1700 cm^{-1} band). The infrared spectrum of the second and final aliquot, removed after 43 hours, displayed bands at 3530 cm^{-1} (medium and broad), 3078 cm^{-1} (weak), 1690 cm^{-1} (strong), and 1645 cm^{-1} (strong). These latter two bands are not readily interpretable in terms of CXXX. It is very unlikely that the band at 1690 cm^{-1} arises from hydrolysis of the ethylenedioxy group to the corresponding ketone since

this is only accomplished by treating CVIII with dilute hydrochloric acid at room temperature for 8 hours. The infrared spectrum of this ketone CXXXIII displayed bands at



CXXXIII

3080 cm^{-1}; 2875, 2815, 2780, 2710, 2685 cm^{-1}; 1710 cm^{-1}; 1638 cm^{-1}, clearly different from the reaction product in question. The most tempting explanation of these two bands is the suggestion that they may arise from an α,β-unsaturated carbonyl system. Such a system could conceivably form from LII by a type of dehydration of the hydroperoxide as shown in equation 46 to form the aldehyde CXXXIV. The olefin is

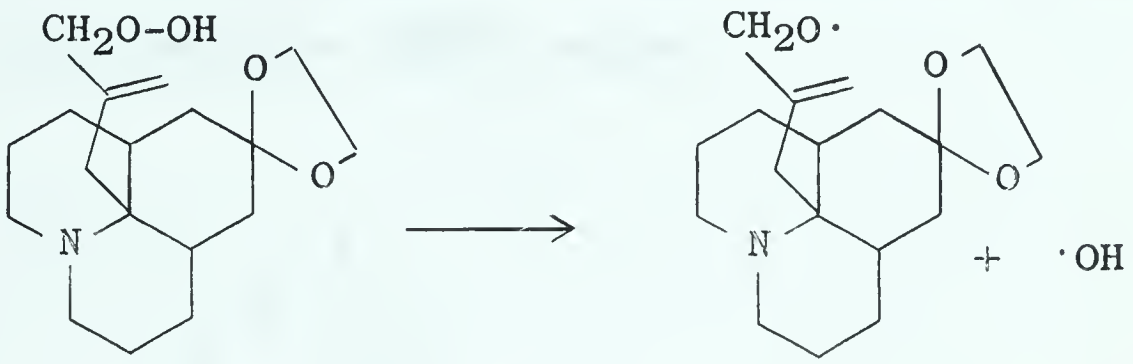


(46)

LII CXXXIV

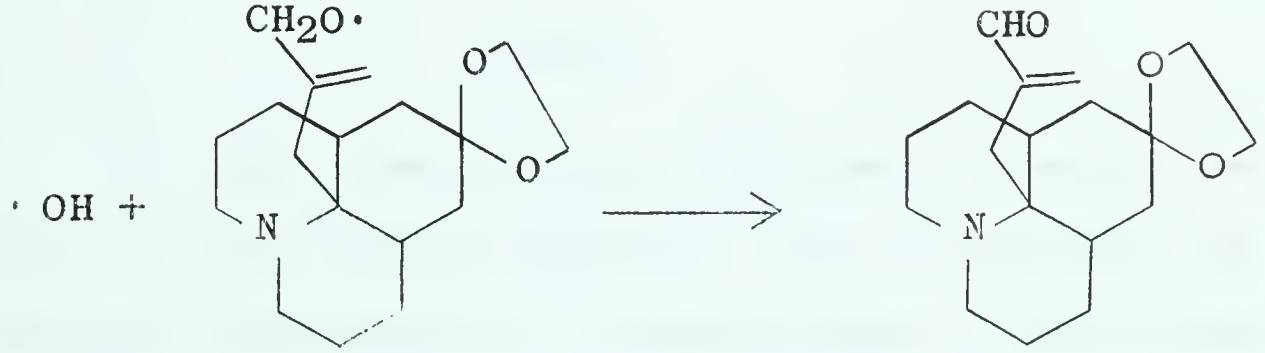
written as an exo-methylene since the infrared spectrum of the reaction product displays a band at 3080 cm^{-1},

associated with the methallyl olefinic linkage, and not present in the rearranged ketone CXXXV. Another, and perhaps more plausible mechanism for the formation of CXXXIV involves homolytic cleavage of the O-O bond, followed by abstraction of a proton by the hydroxy radical to form the aldehyde, as indicated in equation 47.



LII

(47)

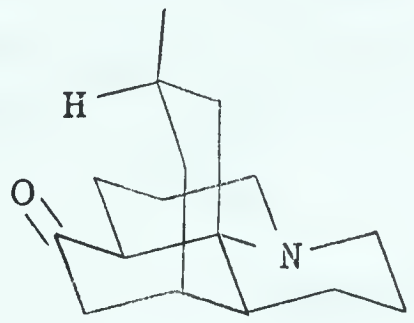


CXXXIV

Further investigation of this line was deferred in favour of researches designed to enable the available all cis CXI to be used in the main series, the synthesis of lycopodine I. Before turning to a discussion of this work however, results of the treatment of CVIII with mineral acid will be given.

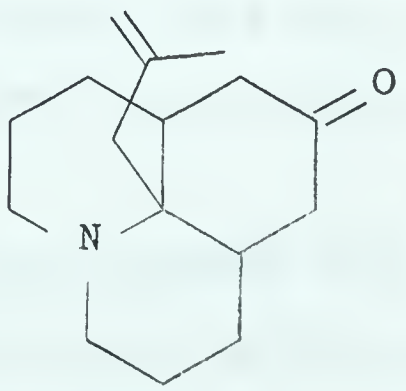
(b) The Prolonged Treatment of CVIII with Hydrochloric Acid

Of the two isomers of CVIII produced in the Grignard reaction, one, CXI, is not suited to undergo ring formation via equation 44. The all trans isomer CX however should be capable of such a reaction after hydrolysis of the ethylene ketal grouping. The product would of course be in the epilycopodine CXXXVI series.



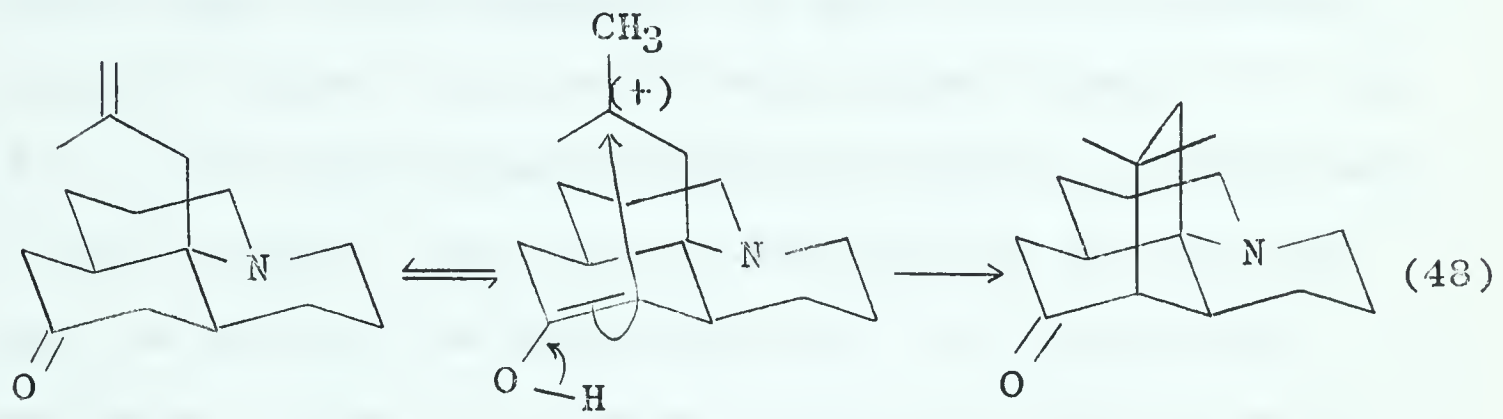
CXXXVI

The first reaction carried out on CX was, as the title of this section implies, the treatment of the single component obtainable by chromatography of the product of the Grignard reaction of XCVIII with CVII with hydrochloric acid. The immediate result of such treatment will be the hydrolysis of the ethylenedioxy group to form the ketone CXXXIII.



CXXXIII

It might however be expected that a further reaction would occur, between the enol form CXXXVIII of CXXXVII and the protonated double bond of the methallyl chain. This would in all likelihood lead to the formation of a compound containing a five-membered bridge-ring, as shown in equation 48.



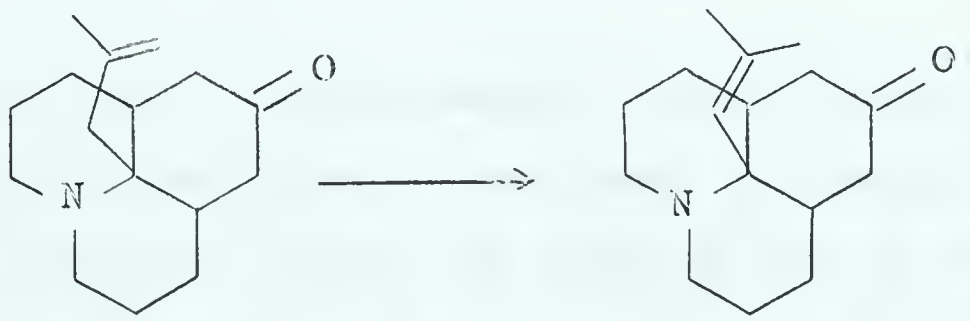
(48)

CXXXVII CXXXVIII CXXXIX

At this point it must be noted that when this treatment with acid was being considered, the unusual behaviour of the isomers CX and CXI on column chromatography was not realized. Hence, by analogy with the unsubstituted hexahydrojulolidines (58) it was felt that the single component isolated, being the more polar, was the all trans CX. Only after the reaction was performed and the structure of the product elucidated was it realized that we had been dealing with the all cis isomer CXI, where of course there was no chance of reaction as shown in equation 48.

When CXI was treated with 10-15% hydrochloric acid at reflux for 5 days, an oil was obtained, which slowly crystallized, and contained only one component, as

indicated by thin layer chromatography. The infrared spectrum (Figure 7) of this substance displayed absorption at 2870, 2820, 2780, 2745, 2700 cm^{-1} (Bohlmann bands), 1710 cm^{-1} (keto carbonyl), and 1645 cm^{-1} (olefin). The band at 3072 cm^{-1} in CXI had disappeared. The n.m.r. spectrum (Figure 18) contained maxima at τ 8.32 (doublet, J=0.75 cps), τ 8.20 (doublet, J=1 cps), τ 4.48 (broadened singlet), as well as several broad bands between τ 7.9 and τ 6.7. It is thus clearly indicated that an olefinic bond is still present, but the disappearance of the 3072 cm^{-1} band, as well as the down-field shift of the olefinic resonance in the n.m.r. serve to show that the material is not CXXXVII. The n.m.r. integration of the first three peaks quoted above is in the approximate ratio 3:3:1, suggesting the presence of a structure of the type $CH_3-\overset{CH_3}{\overset{|}{C}} = \overset{H}{\overset{|}{C}}-$. Thus the experimental results can be interpreted in terms of a double bond migration, indicated in equation 49, to produce the new keto-olefin CXXXV. The



(49)

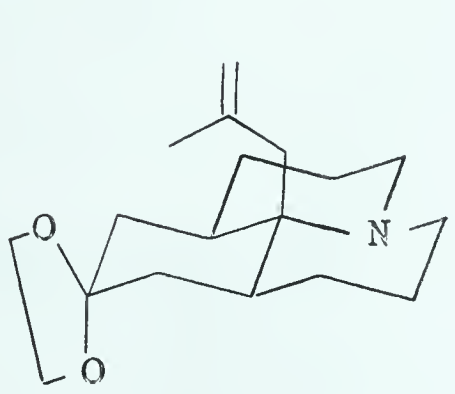
CXXXIII CXXXV

possible presence of any CXXXIX, arising as in equation 48 or by a similar closure of CXXXV is eliminated by the presence of only one component in the reaction product. Any

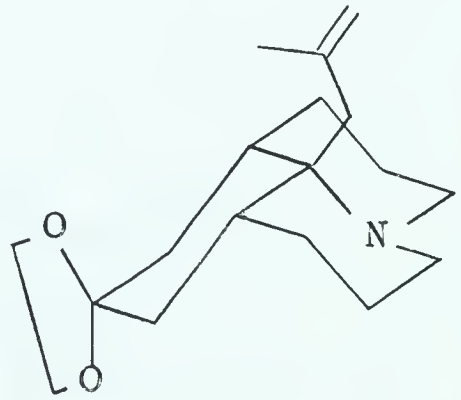
remote possibility of the occurrence of a reverse Mannich reaction to yield XCIX and isobutylene can be ruled out on two grounds. First, the olefinic linkage of XCIX is not demonstrable by n.m.r. analysis, as it is in CXXXV and secondly, the mass spectrum (Figure 27) of this reaction product displayed a parent peak at m/e 247, the mass to charge ratio expected for a compound of the structure CXXXV.

7. The Introduction of Unsaturation at Carbon-7a

Since the predominant isomeric form of CVIII was the all cis structure CXI, and since the desirable all trans



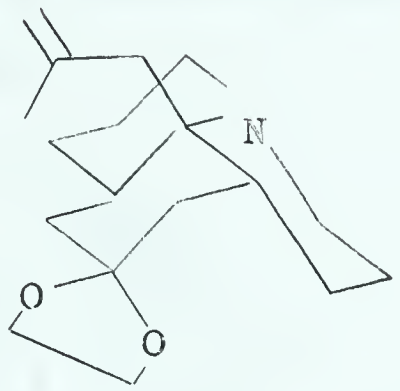
CX



CXI

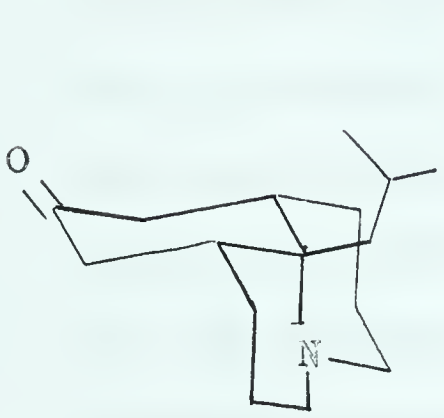
CX, though formed in small amounts, could not be isolated in pure form, consideration was given to finding a way in which the available isomer CXI could be put to profitable use. It is of course the stereochemistry of CXI which makes it unsatisfactory since the C-11 substituent is oriented equatorially to the ring in which cyclization must occur. This situation could be remedied if one of the hydrogens at C-7a or C-10a could be epimerized and the central ring inverted resulting in the production of CXII, the cis-trans

isomer where now the C-11 chain is axial to the appropriate ring. Isomer CXII has as well the lycopodine I stereochemistry.

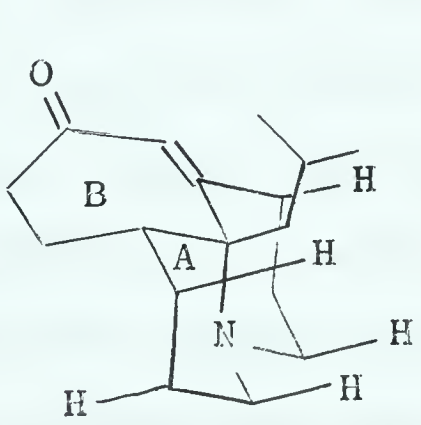


CXII

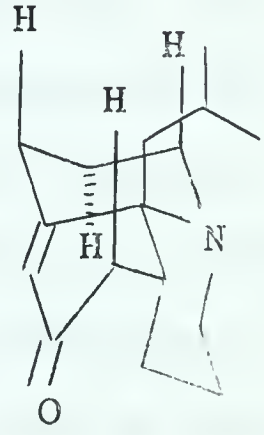
It was felt that this might possibly be accomplished via the ketone CXL. Introduction of unsaturation at carbons



CXL



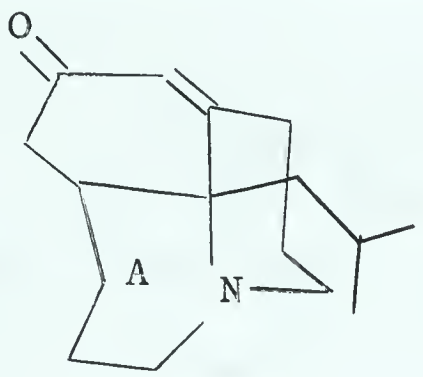
CXLI



CXLII

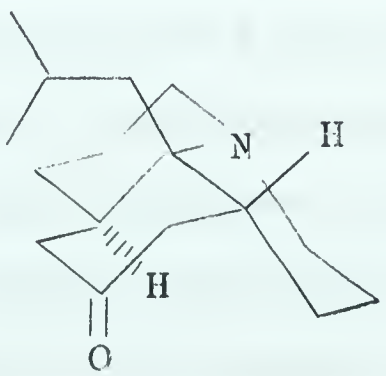
7a-8 would lead to the ketone CXLI. Because of the conformational mobility of the nitrogen atom, it should be possible for CXLI to assume the alternate conformation CXLII. This change will involve an inversion of the nitrogen to form a boat ring A, and a flip of this boat into a new chair form with simultaneous transformation of ring B from one half-chair form to the other. The energy barrier between these two forms should not be unduly high, and perhaps may be only slightly greater than that between two

chair forms of a cyclohexane ring, since the most strained conformation between CXLI and CXLII is that in which ring A is in the boat form (CXLIII). The fact that this conformational mobility is possible does not however ensure



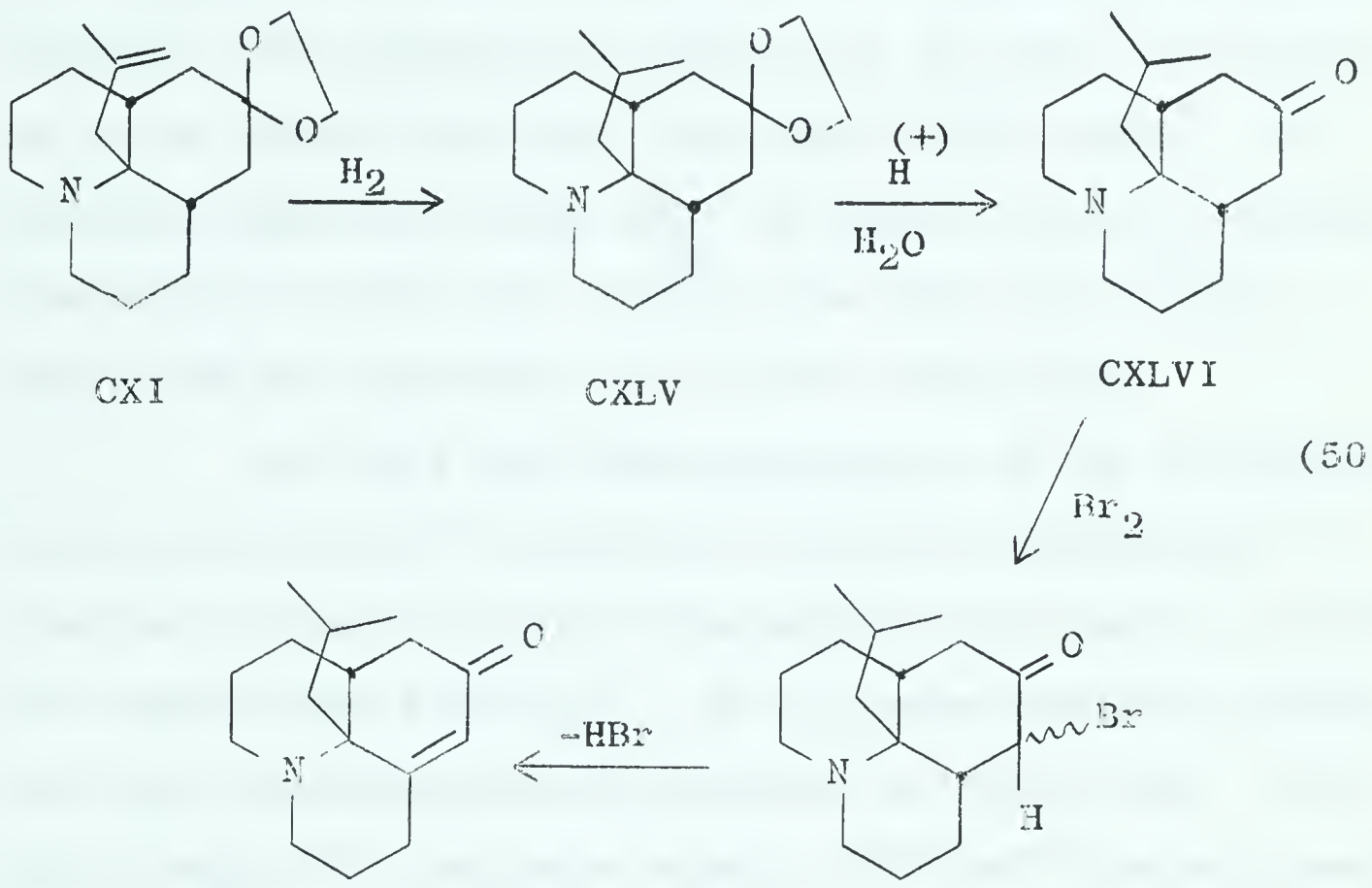
CXLIII

that, of the two possible forms, CXLII will be preferred. Inspection of models shows that CXLI has five 1,3-diaxial substituent-hydrogen interactions, whereas CXLII has only four, and thus it was felt that CXLII might indeed be the preferred conformation. Since CXLI should show Bohlmann bands while CXLII should not, a method is available whereby the two conformations may be distinguished. Reduction of the unsaturated ketone by dissolving metal would then be expected (60) to lead to CXLIV, which possesses the desired cis-trans stereochemistry.



CXLIV

The method whereby it was vizualized that this new unsaturation would be introduced is a fairly conventional one, and is shown in equation 50. The first step, the catalytic reduction of CXI is included to avoid bromination of the olefinic linkage in a later stage.



The catalytic reduction of CXI proceeded uneventfully to produce a viscous oil (b.p. 125°/2.5 mm), later a colourless crystalline solid (m.p. 51-53°C.). Thin layer chromatography of the reduction product showed that it consisted of a single component, different from the starting material. The infrared spectrum (Figure 8) of this material displayed no olefinic absorption and the band centered at τ 5.11 in the n.m.r. spectrum of CXI, associated with the

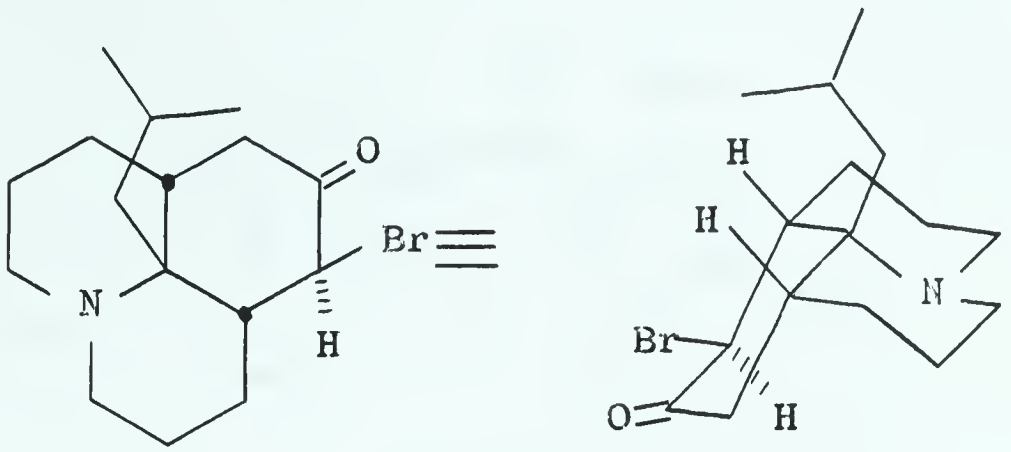
olefinic protons, had similarly disappeared from the n.m.r. spectrum of the reduced material. Since the mass spectrum (Figure 26) provided no parent peak, it neither supported nor argued against the assignment of structure CXLV to the reduction product. On the basis of the spectral evidence and the mode of formation, such an assignment seems well founded. The perchlorate derivative of CXLV was prepared as white cubical crystals (m.p. 297-299°C. dec.). The infrared spectrum (nujol mull) of these crystals displayed absorption at 3105 cm^{-1} ($-\overset{(+)}{N}-H$), and 1105 cm^{-1} ($\overset{(-)}{ClO_4}$). There was no indication of olefinic absorption.

The acid catalyzed hydrolysis of the 9-ethylene-dioxy group of CXLV similarly proceeded uneventfully to yield a viscous oil which crystallized upon gentle scratching, to a colourless semisolid. The infrared spectrum (Figure 9) of these crystals showed absorption at 2870, 2812, 2780, 2700, 2685 cm^{-1} (Bohlmann bands), 1702 cm^{-1} (keto-carbonyl), and 1422 cm^{-1} ($-CH_2-$ adjacent to a carbonyl). The mass spectrum (Figure 25) while displaying only a very small peak at m/e 249, did contain a very strong peak at m/e 192, and no peaks at m/e 293 or m/e 236. As is discussed more fully in the next section the presence of the m/e 192 peak is accounted for in terms of the presence of a compound with structure CXLVI, and the absence of peaks at m/e 293 and 236 in terms of the absence of CXLV in the hydrolysis product. Preparation of the hydrobromide salt of CXLVI by treating an ethereal solution of the base with anhydrous hydrogen bromide yielded an off-white powder whose infrared

spectrum (nujol mull) displayed no Bohlmann bands, but did contain absorption at 2705, 2680, 2600 cm^{-1} ($-\overset{\oplus}{N}-H$), and 1694 cm^{-1} (keto-carbonyl). The perchlorate derivative was also prepared, yielding white sugary crystals (m.p. 268-270°C. dec.). The infrared spectrum of this salt displayed absorption at 3100 cm^{-1} ($-\overset{\oplus}{N}-H$), 1698 cm^{-1} (keto-carbonyl), and 1050 cm^{-1} ($\overset{(-)}{ClO_4}$).

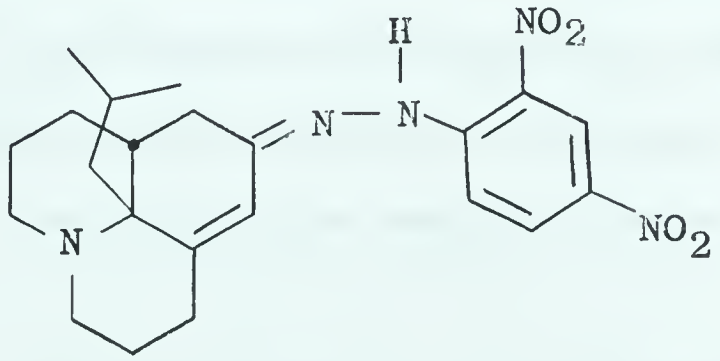
The bromination of CXLVI was carried out using the procedure of Ayer and co-workers (7) who found that the presence of a basic nitrogen interfered with the expected course of the bromination of lycopodine I. By modifying the procedure in such a way that brominations were carried out on the preformed hydrobromide derivative, these workers found that the desired bromo derivative of lycopodine could be prepared in good yield. Correspondingly, the bromination of CXLVI was carried out on a chloroform solution of CXLVI, to which had previously been added sufficient chloroform saturated with hydrogen bromide to ensure that all the base was in the form of its hydrobromide salt. After addition of the bromine, work-up gave a light yellow solid in 85% yield. This product gave a positive Beilstein test for halogen, and thin layer chromatography showed the presence of a major constituent different from starting material, plus a trace of substance with an R_f corresponding to CXLVI. The infrared spectrum (Figure 10) of this solid displayed absorption at 2875, 2822, 2780, 2690 cm^{-1} (Bohlmann bands), 1745 cm^{-1} (shoulder), and 1730 cm^{-1}. The shift of the carbonyl frequency to higher wave numbers on formation of an

α-halocyclohexanone is due to the introduction of equatorial halogen (44). Thus structure CXLVII is assigned to the bromination product.



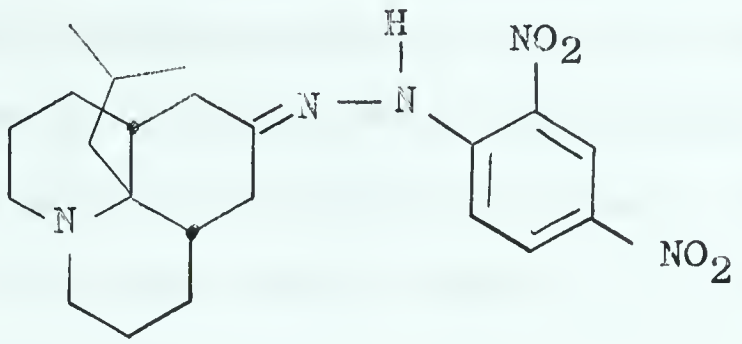
CXLVII

The presence, and position, of the bromine atom in CXLVII was further demonstrated by formation of the 2,4-dinitrophenylhydrazone derivative CXLVIII of CXLVII. This was prepared by refluxing the base in acetic acid solution with one equivalent of the hydrazine. Basification of the red solution yielded a reddish orange powder whose ultraviolet spectrum, measured in 95% ethanol (aldehyde free) showed an intense maximum at 372mμ. This indicates the presence of an α,β-unsaturated hydrazone (14a), i.e., CXLVIII. A parallel reaction using CXLVI produced a similar



CXLVIII

reddish orange powder whose ultraviolet spectrum however, displayed a maximum at 361mμ this time typical of a saturated hydrazone (47), i.e. **CXLIX** . On the basis of



CXLIX

this evidence, and the infrared spectrum of the bromo compound, structure CXLVII may be assigned to that substance.

Attempts were now made to prepare the α,β-unsaturated ketone CXLI by dehydrobrominating CXLVII. Methods tried were refluxing CXLVII with 2,4,6-trimethylpyridine or 2,6-dimethylpyridine, treatment with alcoholic potassium hydroxide, and reaction with lithium bromide-lithium carbonate-dimethylformamide. These reactions were all uniformly unsuccessful in the production of recognizable olefinic material, a situation reminiscent of the similar reactions attempted on LXXXI. It is possible that the difficulties experienced with CXLVII are at least in part due to the presence of equatorial halogen which would not be expected to eliminate as readily as the axial epimer.

8. The Mass Spectra of Representative Hexahydrojulolidine Derivatives.

Recently, MacLean (61) has studied the behaviour

of a large number of the Lycopodium alkaloids under electron impact in a mass spectrometer and has interpreted the resulting spectra in terms of several basic fragmentation schemes. Similar studies were carried out by Law (62). The spectrum of dihydrolycopodine (CL) for example, displays prominent peaks at m/e 249 (M+), 192 (M-57), 174 (M-75), and 146 (M-103) as well as a number of others. MacLean (61) proposed the following scheme (Chart 1) to explain the

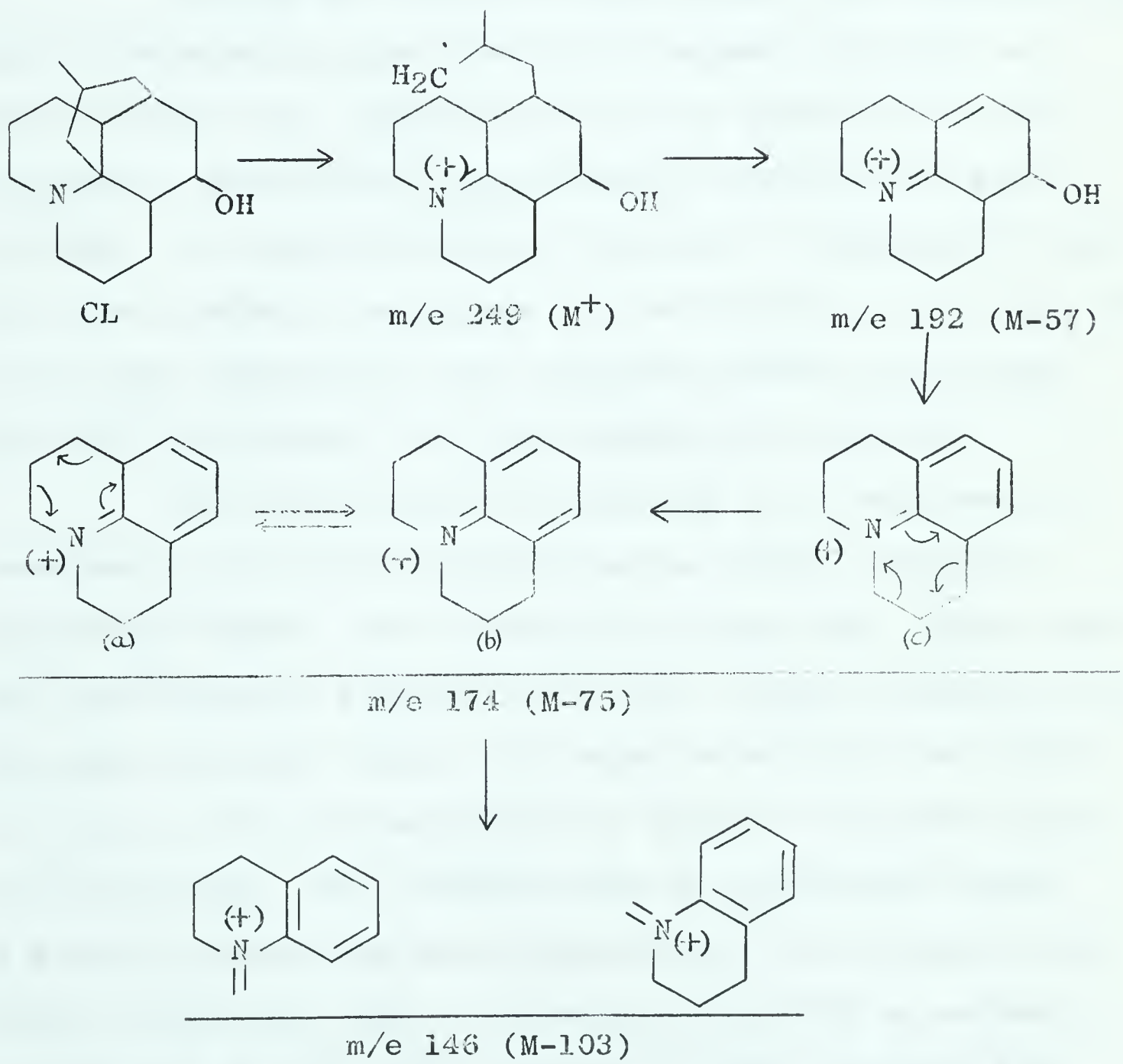


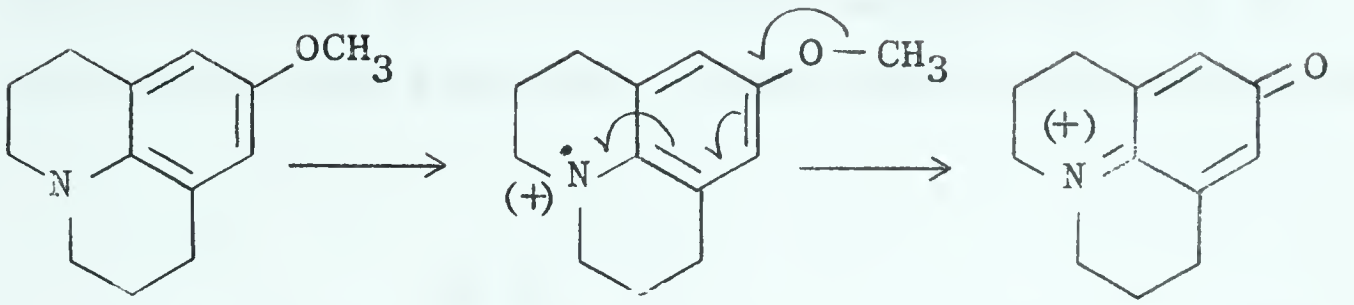
Chart 1

The Fragmentation of Dihydrolycopodine CL

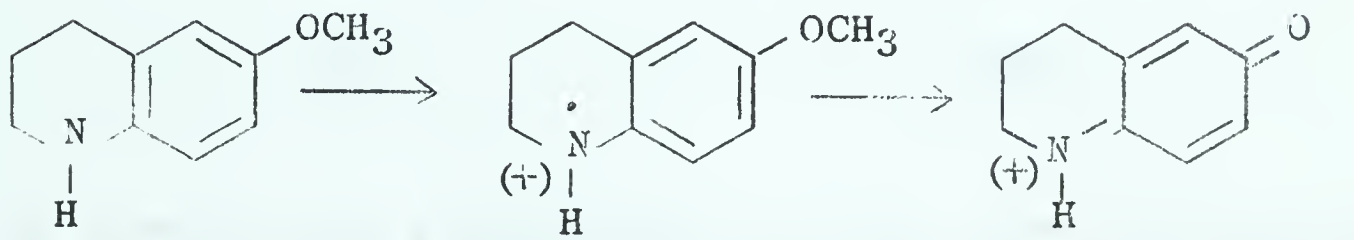
presence of these 4 peaks, which well illustrates the commonly observed fragmentation pattern of many of the tetracyclic Lycopodium alkaloids. Generally speaking the strongest peak in the spectrum corresponds to the loss of the bridge-ring, in the case of dihydrolycopodine CL, m/e 192. Furthermore in those compounds carrying a readily eliminated group in ring B, a peak at m/e 174 and m/e 146 are observed.

During the course of the present work occasion was had to measure the mass spectra of several related, but structurally less complex, julolidines generally for the purpose of determining the molecular weight of the substances. It was felt to be of interest to examine the spectra of these synthetic compounds in more detail, in the hope that they would substantiate the proposed schemes and perhaps provide new evidence for the fragmentation process.

The first group of compounds to be examined are 6-methoxy-1,2,3,4-tetrahydroquinoline XCIII, 9-methoxy-julolidine XXVIII, and 9-hydroxyjulolidine XCV. Their spectra are reproduced in Figures 19, 20, 21. As can be readily seen, the most prominent peak in the spectra of XCIII and XXVIII is that at M-15, corresponding to loss of the methyl group from the ether. The fragmentation is illustrated below. A similar pattern has been observed for the analogous compound p-anisidine (63). The behaviour of XCV is entirely parallel in that the mass spectrum of this compound displays a very intense peak at m/e 188 (M-1) corresponding to loss of the phenolic hydrogen atom as is indicated below.

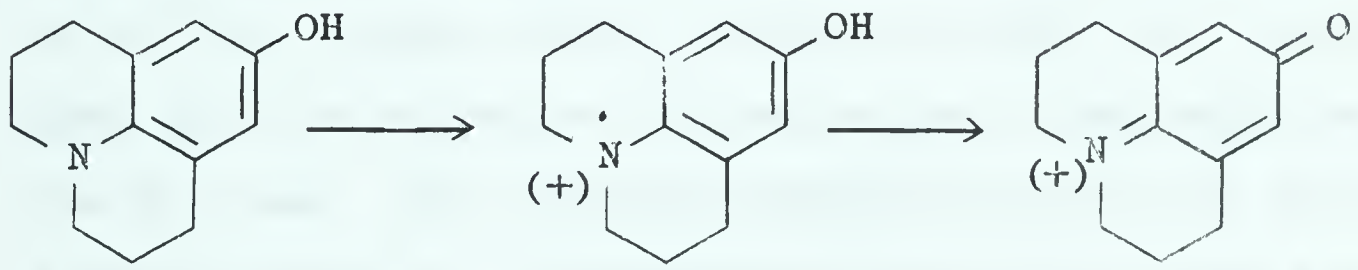


XXVIII m/e 203 m/e 188 (M-15)



XCIII m/e 163 m/e 148 (M-15)

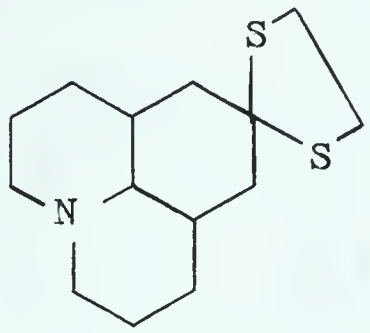
The presence of a further strong peak at m/e 160 indicates the loss of C=O and/or ethylene from ion m/e 188.



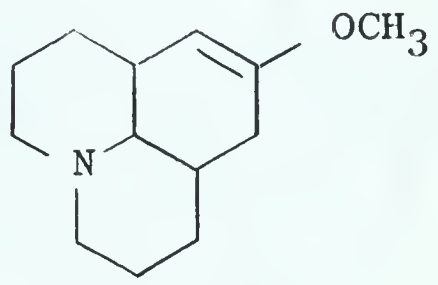
XCV m/e 189 m/e 183

The second group of compounds are two derivatives of 9-keto-7a,8,9,10,10a,11-hexahydrojulolidine, namely the enol-methyl ether XCVI and the ethylene thioketal XCI.

Their spectra are reproduced in Figures 24, 22. As is the case with most of the julolidine derivatives and the lycopodine type alkaloids, these spectra are distinguished



CLI



XCVI

by a relatively strong peak at a m/e number corresponding to loss of the substituent attached to carbon 11, which is an hydrogen atom in XCVI and CLI. The compound XCVI also displays a very intense peak at m/e 192 (M-15), corresponding to loss of the methyl group of the ether. This, it will be recalled was also the chief mode of fragmentation of XXVIII and XCIII. The proposed origin of these peaks, as well as several others is given in Chart 2. It can be seen that the molecular ion may arise in two ways, as may the M-1 peak. The proposed fragmentation of CLI is outlined in Chart 3. An interesting feature of this spectrum is the occurrence of relatively intense peaks at m/e 174, 175, and 176. As can be seen from the chart, the proposed scheme to explain this results in the production of two different ions of m/e 174, and consequently of m/e 146.

Turning now to those hexahydrojulolidine derivatives substituted at carbon-11, we find that these

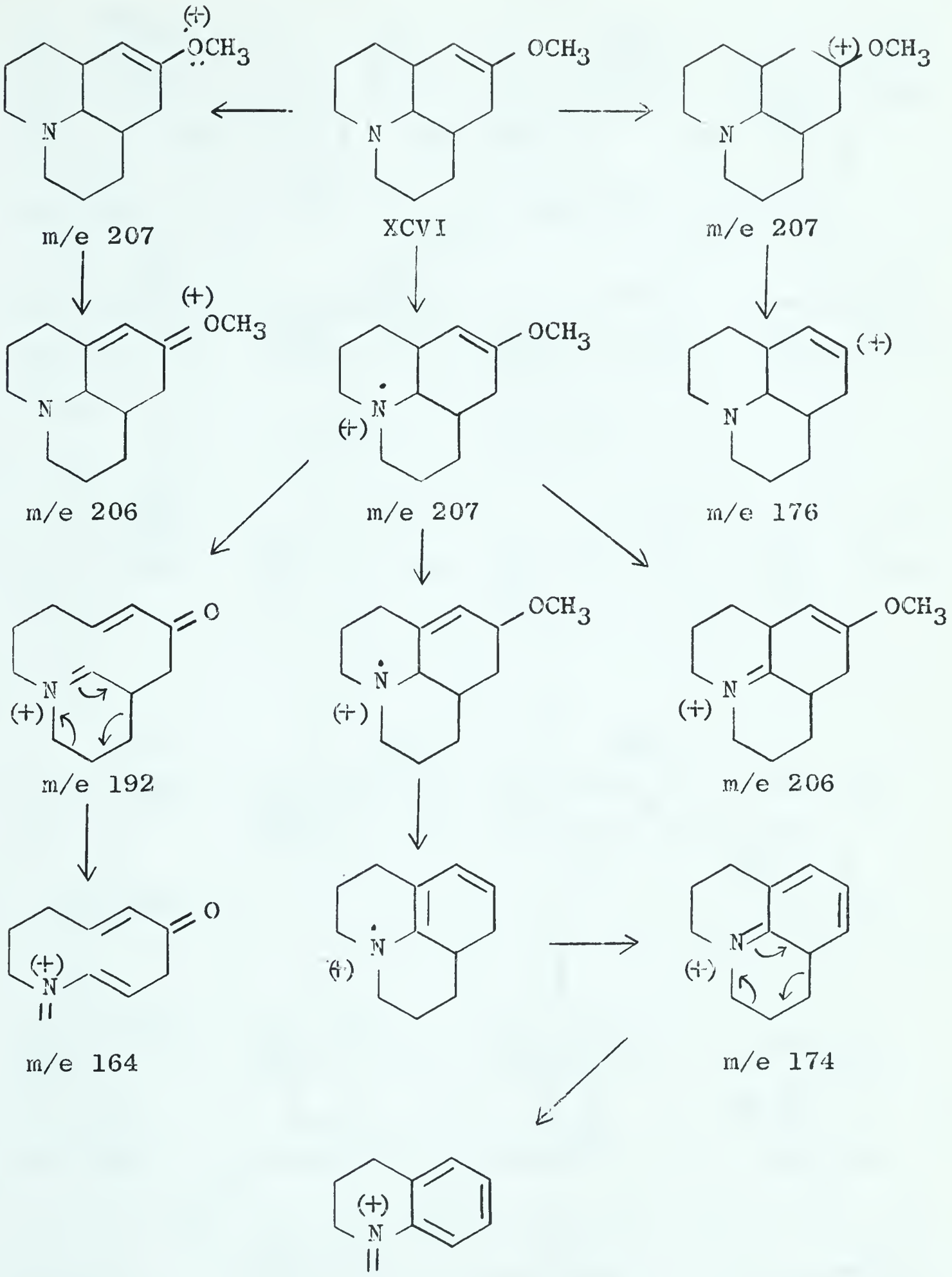


Chart 2

The Fragmentation of 9-Methoxytetrahydrojulolidine XCVI

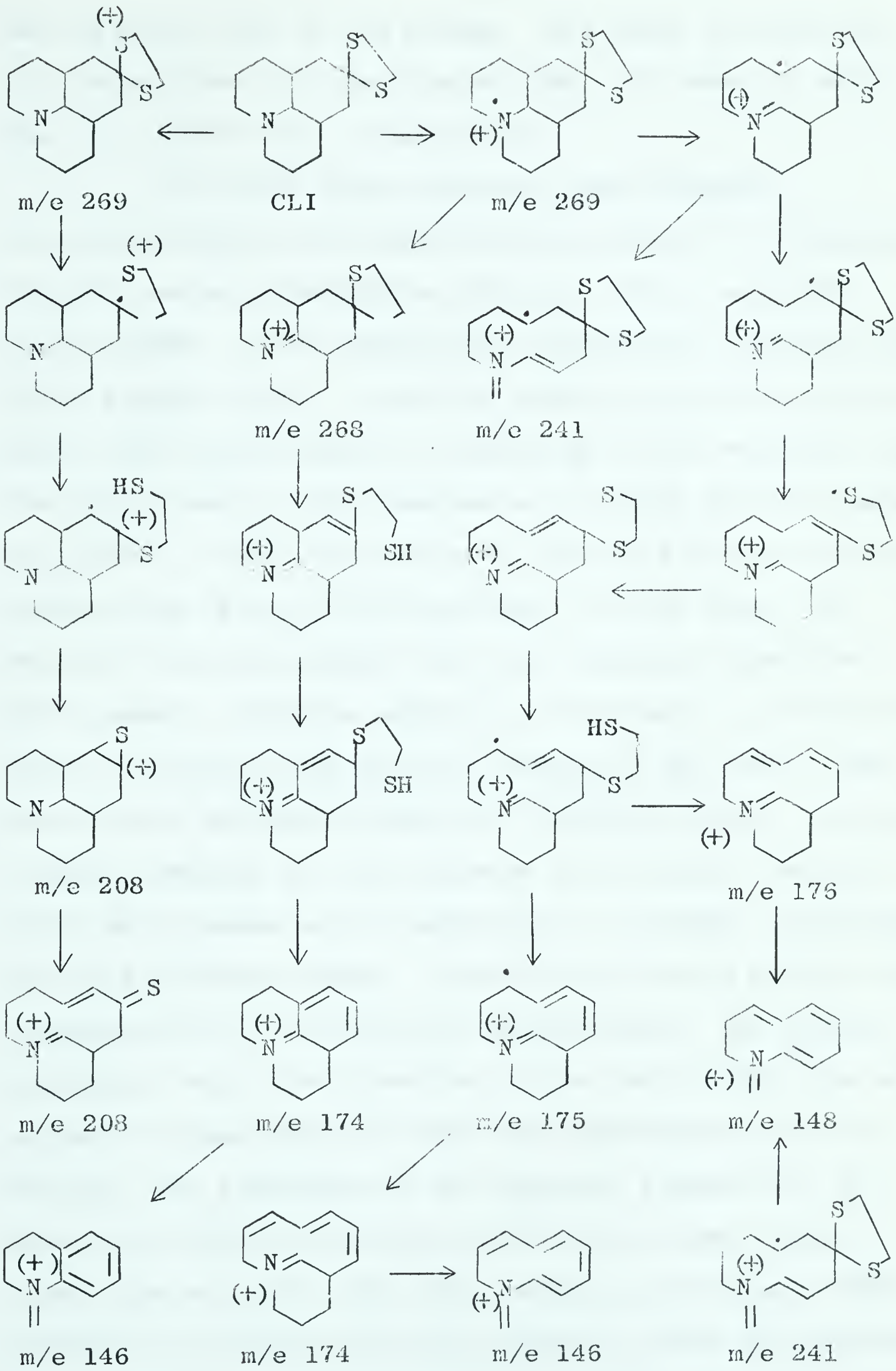


Chart 3

The Fragmentation of the Ethylenethioketal CLI

may be dealt with in two groups: (a) those in which the C-11 substituent is unsaturated, and (b) those in which the C-11 substituent is saturated.

The first group contains three members, 9-ethylenedioxy-11-allylhexahydrojulolidine CV, 9-ethylene-dioxy-11-methallylhexahydrojulolidine CVIII, and keto-olefin CXXXV. Their spectra are reproduced in Figures 28, 23,27 respectively. It will be noted at once that neither CV or CVIII show a peak corresponding to the molecular ion. The first peak of any consequence in either spectrum appears at m/e 236. This can readily be explained by postulating facile loss of the C-11 substituent in both cases, as MacLean (61) has proposed for the lycopodium alkaloids. This process should be especially favourable in CV and CVIII since not only is the positive charge of the ion m/e 236 distributed between nitrogen and tertiary carbon, but the radical produced via the cleavage is an allylic radical. Other major peaks may be explained by a further invocation of the lycopodine scheme. Thus Charts 4 and 5 outline the fragmentation of CV and CVIII respectively. The schemes postulate that after formation of the ion m/e 236, the sub-sequent fragmentation of these two substances should be similar, and inspection of the spectra, Figures 28, 23 show that they are virtually identical at mass numbers lower than m/e 236. The third member of the group, CXXXV presents a slightly different problem in that the ethylene-ketal group, previously present, is replaced by the original ketone, and the methallyl double bond is now α to carbon-11.

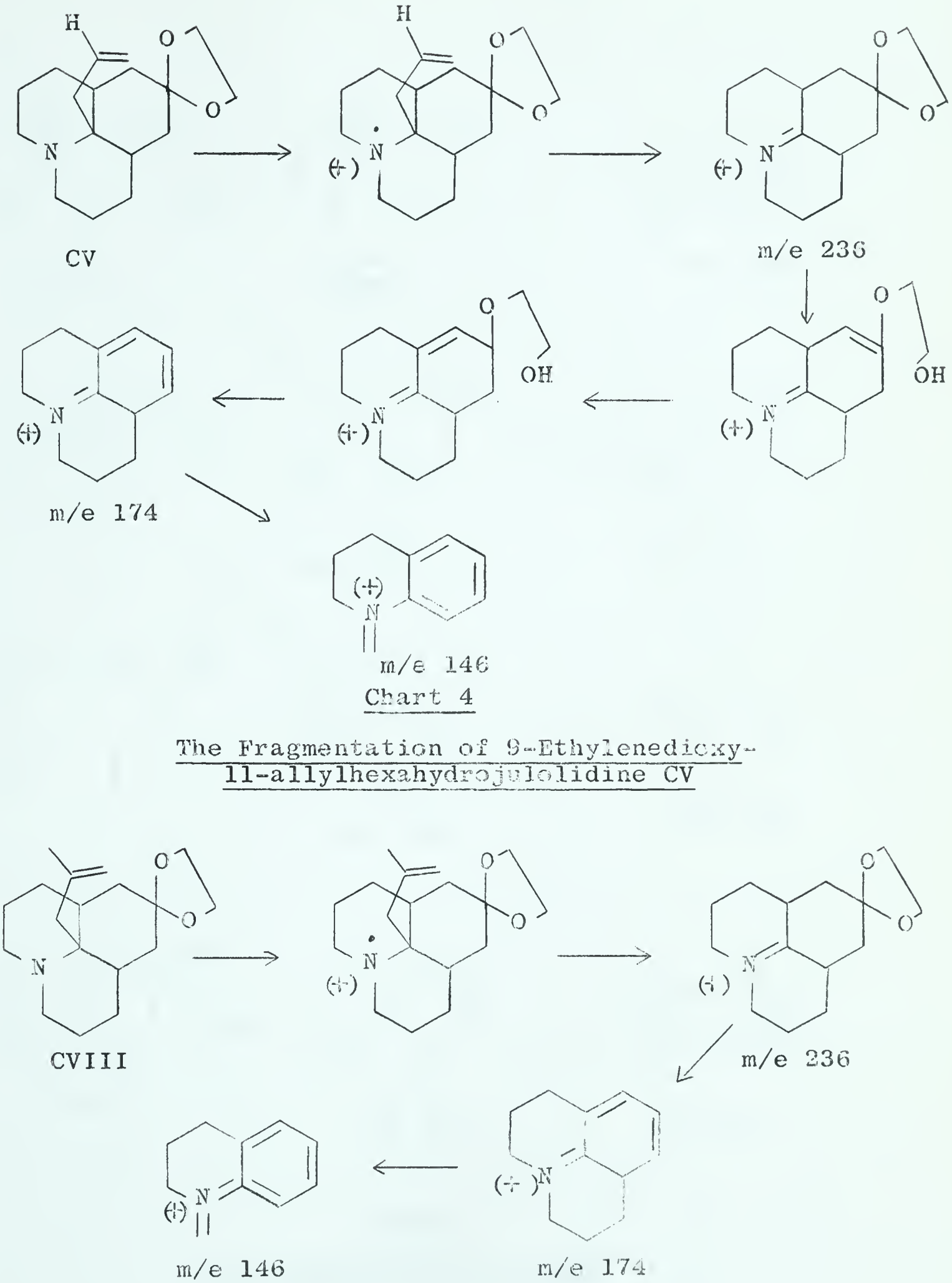


Chart 4

The Fragmentation of 9-Ethylenedioxy-11-allylhexahydrojulolidine CV

Chart 5

The Fragmentation of 9-Ethylenedioxy-11-methallylhexahydrojulolidine CVIII

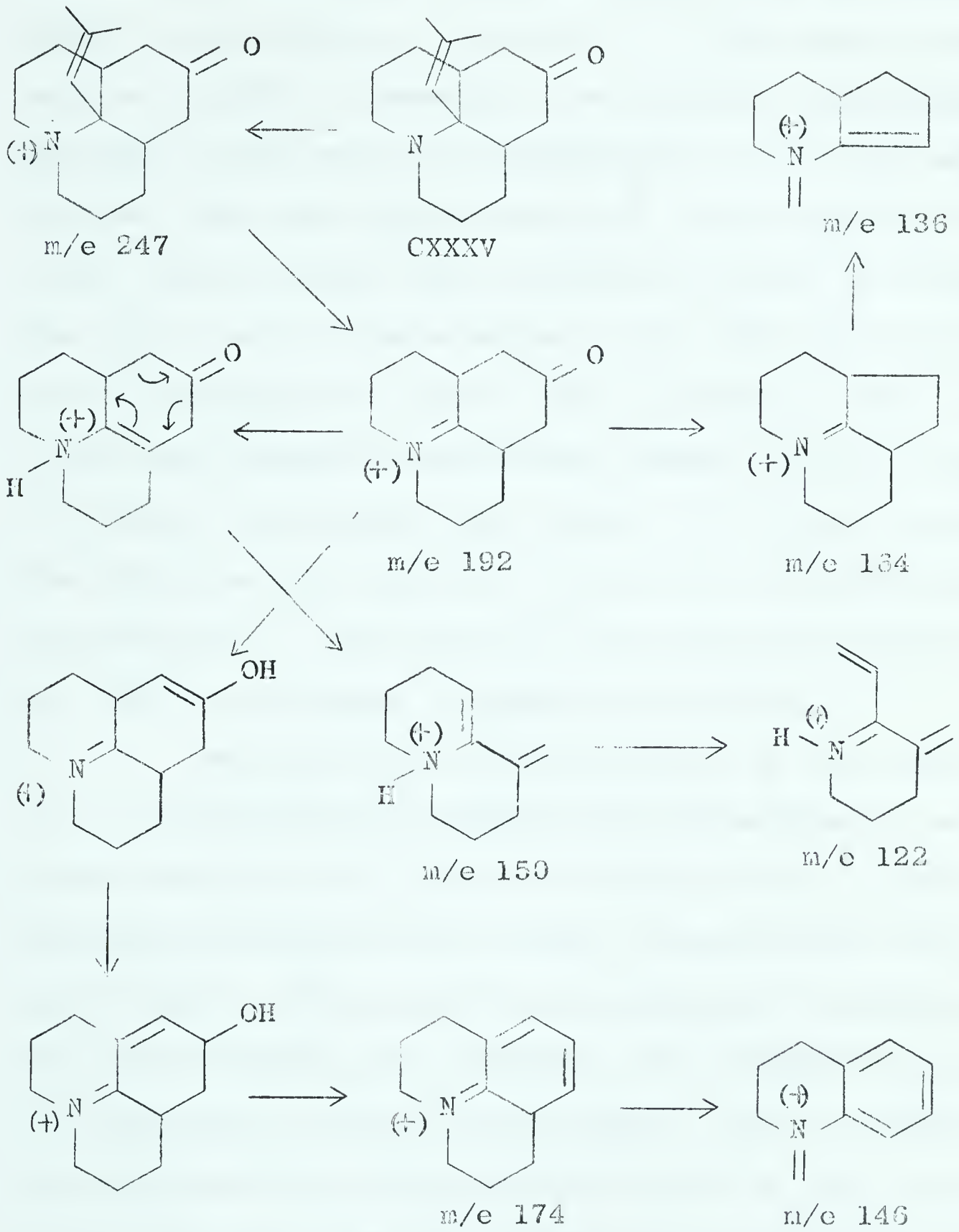


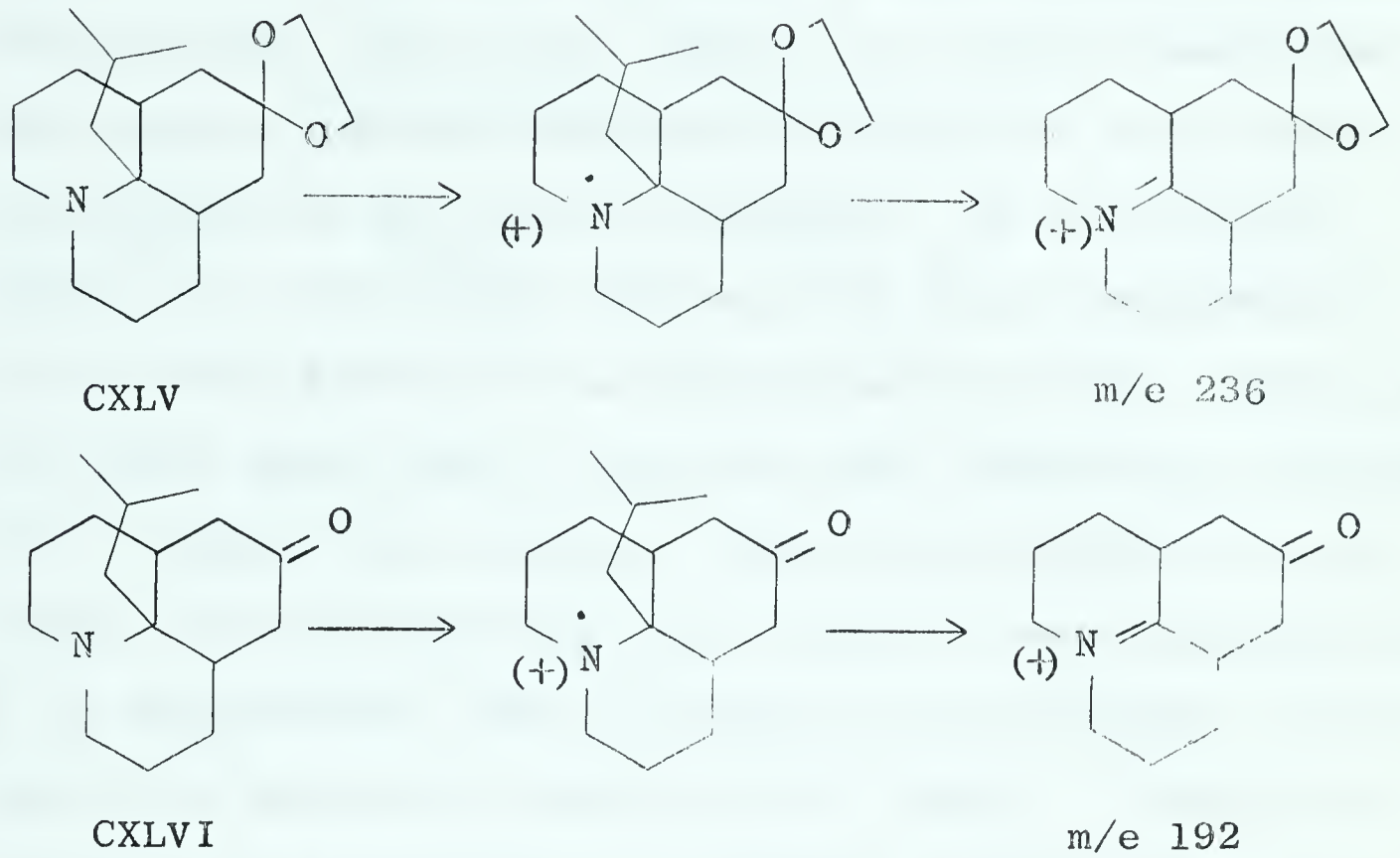
Chart 6

The Fragmentation of CXXXV

It is found that loss of the C-11 substituent still occurs but not as readily as in CV and CVIII. The spectrum of CXXXV is reproduced in Figure 27. In this case a parent peak at m/e 247 is observed, its presence reflecting a decrease in the ease of fragmentation of the C-11 substituent when the double bond is β to the nitrogen (a vinyl radical rather than an allylic radical is produced). The major peak in the spectrum at m/e 192 (M-55) nevertheless corresponds to loss of the C-11 chain. Chart 6 outlines the proposed fragmentation scheme for this compound, accounting for all the major peaks. It is to be noted that the characteristic ions m/e 174 and 146 are obtainable by this sequence. The nature of the ions giving rise to the m/e 150 and 122 peaks is highly speculative.

We now turn to the discussion of the mass spectra of two derivatives of hexahydrojulolidine bearing saturated substituents at C-11, namely 9-ethylenedioxy-11-isobutyl-hexahydrojulolidine CXLV and the corresponding 9-keto compound CXLVI. Their spectra are reproduced in Figures 26, 25. As in the previous examples, the fragmentation of these two compounds is dominated by loss of the C-11 substituent, as evidenced by an intense peak at M-57 in both spectra. After this loss, further fragmentation should be identical with that of the corresponding unsaturated derivatives below m/e 236 and 192 respectively. Comparison of the appropriate figures shows this to indeed be the case. It is not therefore necessary to indicate the fragmentation of these two compounds CXLV and CXLVI, in any detail, except

to show loss of the C-11 substituent. This is indicated in Chart 7.



CXLV

CXLVI

Chart 7

The Fragmentation of CXLV and CXLVI

To sum up, the fragmentation of the various C-11 substituted hexahydrojulolidines has as its primary process the cleavage of the C-11 substituent. Directions taken from this point are controlled by the nature of the function at C-9, but can be rationalized by a small number of basic schemes. Perhaps the most interesting new fragmentation is that encountered in the loss of methyl from the enol ether XCVI, a process shown in Chart 2.

EXPERIMENTAL

Unless otherwise indicated, infrared spectra were measured on Perkin-Elmer 21, 221, or 421 infrared recording spectrometers; the n.m.r. spectra on a Varian Associates A-60 nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard; the ultraviolet spectra on a Cary Model 14M Recording Spectrophotometer; and the mass spectra on an Associated Electrical Industries Ltd. Model MS-2H (Mod.) recording mass spectrometer equipped with a heated inlet system. The melting points are uncorrected. The infrared and n.m.r. spectra were determined by R. N. Swindlehurst, Mrs. G. Conway, and associates; the mass spectra by Messrs. W. Duholke and R. Taylor. Elementary analyses were performed by C. Daessle in Montreal and F. Pascher in Bonn.

A. THE CYCLOHEXANONE-TYPE MODEL SERIES

1. The Michael Addition of Ethylacetoacetate to 2-Cyclohexen-1-one.

Sodium (1.3 gm, 0.06 mole) was dissolved in anhydrous ethanol (100 mls). To this solution was added ethylacetoacetate (26 gm, 0.2 mole) and 2-cyclohexen-1-one (10 gm, 0.1 mole). The clear colourless solution was stirred at room temperature, with protection against moisture, for 96 hours. The reaction was then diluted with several volumes of water, and extracted with diethyl ether ("ether"). Drying the ether extracts with anhydrous magnesium sulphate, and removing the ether in vacuo yielded 3.5 gms. of an oily yellow solid, which was subjected to column chromatography

over alumina. The results of the chromatogram are summarized in Table 3. Recrystallization of fraction 2 from ethyl

Table 3

Chromatography of the Products of Michael Addition

Fraction	Eluent	Yield gm.	Prominent IR Bands cm^{-1}
1	1:1 Ether/Benzene	0.597	3580, 3420 1705 (broad)
2	7:3 Ether/Benzene	2.11	3350, 1725, 1704
3	4:2 Ether/Benzene	0.262	1700, 1640
4	4:2 Ether/Benzene	0.691	3590, 3440, 1720, 1638, 1605

acetate gave pure white crystals (m.p. 136-137°) whose infrared spectrum in nujol had bands at 3355, 1730, 1704 cm^{-1}. This material also gave a negative test with ferric chloride reagent (36). The n.m.r. spectrum (carbon tetrachloride solution) as determined on an HR-60 instrument (37) displayed the following maxima: τ 8.70 (triplet, J=6.5 cps), $-CH_2-\underline{C}H_3$; τ 8.46 (singlet), $-\overset{|}{\underset{|}{C}}-CH_3$; τ 8.35 (broad), $-\underline{C}H_2-$; τ 7.73 (broad), $-\overset{O}{\overset{\|}{C}}-\underline{C}H_2-$; τ 7.46 (singlet); τ 7.32 (broad); τ 7.00 (broad); τ 6.78 (singlet), $-\overset{H}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$; τ 5.78 (quartet, J=7.5 cps), $-O-\underline{C}H_2-CH_3$. Analysis: Calculated for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%; molecular weight 226. Found: C, 64.23, 64.25; H 7.96, 7.80%; molecular weight (Rast) 232. The structure assigned to this product is LXV.

Treatment of fraction 4 with ferric chloride reagent gave a positive test, and structure LXIV is assigned

to it. Prominent bands in the infrared spectrum of this material are listed in Table 3.

2. Basic Hydrolysis of 2-Hydroxy-2-methyl-3-carboethoxybicyclo[2,2,2]octan-6-one (LXV).

Compound LXV (0.0452 gm, 1.98 x 10^{-4} mole) was dissolved in 1/1 distilled water/ethanol (25 mls). To this was added a solution of sodium hydroxide (0.0300 gm, 7.92 x 10^{-4} mole) in distilled water (3 mls). This clear reaction mixture was stirred at room temperature for 24 hours. At the end of this period the reaction was made just acid with dilute hydrochloric acid and extracted with several portions of chloroform. Drying these extracts with anhydrous magnesium sulphate and evaporating the chloroform in vacuo yielded a white solid (0.0335 gm, 87.1%) which gave white crystals (m.p. 225-227° dec) on recrystallization from ethyl acetate. The infrared spectrum of this material (either the crude, or the recrystallized material) displayed bands at 3375 (-OH), 1710 (carboxylic acid), 1695 (keto-carbonyl) cm^{-1}. The structure assigned to this substance, on the basis of mode of formation, is 2-hydroxy-2-methyl-3-carboxy-bicyclo[2,2,2]octan-6-one (LXVII).

3. Pyrolysis of 2-Hydroxy-2-methyl-3-carboxy-bicyclo[2,2,2]octan-6-one (LXVII)

The acid LXVII (0.010 gm, 5 x 10^{-5} mole) was placed in a small centrifuge tube and heated at 230° until effervescence ceased, about 1 1/2 minutes. The dark

coloured oily residue was washed out of the tube with chloroform. Evaporation of this solvent gave a light brown oil (0.008 gm). The infrared spectrum of this oil had bands at 1710 cm^{-1} (broad) (keto-carbonyl), 1410 cm^{-1} ($-CH_2-\overset{O}{\overset{\|}{C}}-$), 1355 cm^{-1} ($CH_3-\overset{O}{\overset{\|}{C}}-$).

4. Preparation of the Pyrrolidine Enamine of Cyclohexanone

This material was prepared as reported in the literature (40). The enamine was obtained quantitatively, as judged by the amount of water eliminated in the reaction. The product was a dark-coloured oil, and attempts to improve the colour by distillation at reduced pressure or column chromatography caused the enamine to decompose. It was found that the substance could be used satisfactorily in the crude state.

5. Preparation of 2-(2-Cyanoethyl)cyclohexanone (LXIX)

This material was prepared as reported in the literature (40). The cyanoketone was obtained in 100% yield based on the starting cyclohexanone and gave an infrared spectrum with bands at 2244 cm^{-1} (saturated nitrile), 1700 cm^{-1} (keto-carbonyl), 1420 cm^{-1} ($-CH_2-\overset{O}{\overset{\|}{C}}-$).

6. Preparation of 1-Ethylenedioxy-2-(2-cyanoethyl)cyclohexane (LXX)

This material is reported (41) in the literature

but the published method of preparation was unsuccessful in our hands. A satisfactory synthesis was developed after a number of attempts.

2-(2-Cyanoethyl)cyclohexanone LXIX (114 gm, 0.75 mole) was added to a stirred solution of boron trifluoride etherate (150 mls) in ethylene glycol (1000 mls). This dark coloured solution was then stirred at room temperature for 24 hours. Reaction times appreciably less than this result in reduced yields. At the end of this period the reaction was extracted with chloroform, and the extracts washed once with water. Drying the solvent with magnesium sulphate and removing it in vacuo yielded a dark coloured oil (108 gms, 95%) which displayed no carbonyl absorption in the infrared. This oil was distilled in vacuo, and the fraction boiling at 126-128°/2.0 mm collected. The infrared spectrum of the cyanoketal displayed bands at 2242 cm^{-1} (saturated nitrile), 945 and 920 cm^{-1} (ethylene ketal).

7. Preparation of 1-Ethylenedioxy-2-(3-aminopropyl)cyclohexane

1-Ethylenedioxy-2-(2-cyanoethyl)cyclohexane LXX (25 gm, 0.13 mole) was added to a stirred suspension of lithium aluminium hydride (3.3 gm, 0.35 mole) in anhydrous ether (250 mls). The addition was accompanied by the production of heat and usually was accomplished in 1 - 1-1/2 hours. The reaction mixture was then refluxed with protection against moisture for 24 hours. At the end of this period the reaction was hydrolyzed with water

according to the formula (64) which requires the consecutive addition of distilled water (1 ml per gram of hydride), sodium hydroxide (15% aqueous, 3 mls per gram of hydride), and distilled water (3 mls per gram of hydride). Use of this method results in the production of an ether solution of the reduced material which requires no further drying. Thus water (3 mls), 15% sodium hydroxide (9.9 mls), and water (9.9 mls) were cautiously added to the reduction mixture. The resulting clear colourless ether solution was removed from a large amount of white granular precipitate by suction filtration. The filter cake was washed well with ether, and the washings and filtrate combined and evaporated. Obtained in this way was a colourless oil (26 gms, 100% yield). Infrared spectral data are as follows:

(a) Pure liquid (as a thin film) 3360, 3285, 1645 cm^{-1} ($-NH_2$); 940, 925 cm^{-1} (ethylene ketal)

(b) Dilute chloroform solution 3350, 1660 cm^{-1} ($-NH_2$), 955, 935 cm^{-1} (ethylene ketal).

Attempts to purify this amine by distillation in vacuo resulted in extensive decomposition. For this reason it was not further characterized, but immediately subjected to acetylation.

8. Preparation of 1-Ethylenedioxy-N-acetyl-2-(3-aminopropyl)-cyclohexane (LXXI)

1-Ethylenedioxy-2-(3-aminopropyl)cyclohexane (20 gms, 0.1 mole) was added to a solution of acetic anhydride (12 gms, 0.12 mole) in anhydrous pyridine (100 mls). The

dark coloured reaction mixture was then stirred at room temperature for 16 hours. The pyridine and unreacted acetic anhydride were then partially evaporated in vacuo. The residue was chromatographed on basic alumina, the material eluted with benzene being collected. This yielded a colourless viscous oil (15.7 gm, 65% yield) whose infrared spectrum displayed bands attributable to a secondary amide at 3290, 3085, 1640, 1540 cm^{-1}, and ethylene ketal at 955, 930 cm^{-1}. The boiling point of this oil was 174-176°/0.8 mm. Attempts to obtain a satisfactory elementary analysis of this amide were not successful, likely because of the presence of small amounts of the related ketone (LXVIII).

9. Preparation of N-acetyl-2-(3-aminopropyl)cyclohexanone (LXVIII)

1-Ethylenedioxy-N-acetyl-2-(3-aminopropyl)cyclohexane (LXXI) (7.6 gm, 0.32 mole) was dissolved in methanol (30 mls) and added to a solution of concentrated hydrochloric acid (1.5 mls) in distilled water (25 mls). The reaction was stirred at room temperature for 36 hours. Shorter reaction times result in lower yields. At the end of this period the reaction was extracted with chloroform, which was dried as usual and evaporated. Obtained in this way was a light yellow oil (6.2 gms, 100% yield), whose infrared spectrum displayed bands attributable to an amide, 3300, 1635, 1540 cm^{-1}; and cyclic ketone, 1700 cm^{-1}. The bands present in LXXI at 950 and 935 cm^{-1}, attributed to the ethylene ketal, are absent in the spectrum of LXVIII.

The 2,4-dinitrophenylhydrazone of LXVIII was prepared as follows. LXVIII (0.2 ml) was added to a solution of 2,4-dinitrophenylhydrazine (1 gm) in diethyleneglycol dimethyl ether, "diglyme," (25 mls). One drop of concentrated hydrochloric acid was then added, followed by methanol (3 mls). This caused the precipitation of the derivative as yellow crystals (0.14 gm), m.p. 201-202° after three recrystallizations from ethanol-chloroform. This material displays ultraviolet absorption at 360 mμ, characteristic of the 2,4-dinitrophenylhydrazone derivatives of saturated ketones (47).

Analysis. Calculated for $C_{17}H_{23}O_5N_5$: C, 54.10; H, 6.10; O, 21.22; N, 18.56%. Found: C, 53.98, 54.19; H, 6.83, 6.98; O, 21.03, 21.17; N, 18.03, 17.97%.

10. Preparation of N-acetyl-2-bromo-2-(3-aminopropyl)cyclohexanone (LXXIX)

The method used for this preparation is one which has been reported (43) for the synthesis of 2-bromo-2-methylcyclohexanone.

LXVIII (1 gm, 5 x 10^{-3} mole) was dissolved in glacial acetic acid (30 mls) and a solution of bromine (0.9 gm, 5.6 x 10^{-4} mole) in glacial acetic acid (20 mls) added dropwise, with stirring, over a period of 20 minutes. The red colour of the bromine was discharged upon mixing with the ketone solution. At the end of the addition, the reaction mixture wasdiluted with water and extracted with several portions of chloroform. The extracts were washed

with saturated aqueous sodium carbonate, and once with water. Drying the chloroform extract with magnesium sulphate and evaporating the solvent in vacuo gave a brown oil (0.8 gm, 57% yield) whose infrared spectrum showed the usual amide bands, and which displayed carbonyl absorption at 1722 cm^{-1}. The bromo compound decomposed during attempts not only at vacuum distillation but also at column chromatography on alumina.

Treatment of the bromo compound with 2,4-dinitrophenylhydrazine under the conditions outlined below yielded deep red crystals of m.p. 204-205° after recrystallization from ethanol-chloroform. The ultraviolet spectrum of this derivative displayed intense absorption at 374 mμ. Infrared spectral data for this compound are given in experiment 12.

11. Preparation of N-acetyl-2-chloro-2-(3-aminopropyl)cyclohexanone (LXXXI)

The method used for the preparation of this compound is one which has been reported (45) for the synthesis of 2-chloro-2-methylcyclohexanone.

Ketone LXVIII (1 gm, 5 x 10^{-3} mole) was dissolved in carbon tetrachloride (25 mls) containing chloroform (10 mls) to ensure homogeneity. Sulphuryl chloride (0.67 gm, 5 x 10^{-3} mole) dissolved in carbon tetrachloride was added dropwise to the vigorously stirred solution over a period of one hour. The reaction was then stirred at room temperature for 7 hours. The reaction was extracted consecutively with 3 portions of water (10 mls each), 2 portions of

of saturated aqueous sodium bicarbonate (10 mls each), and one portion of saturated aqueous sodium chloride (10 mls). Drying the organic solvents with magnesium sulphate and evaporation in vacuo gave a yellow oil (1.0 gm, 83%) with a positive Beilstein test. This product did not survive vacuum distillation, and attempts to form a 2,4-dinitrophenylhydrazine derivative in the usual way resulted in the formation of dark gums. The infrared spectrum of the chloro compound displayed absorption at 3260, 3050, 1650, 1540 cm^{-1} (amide), and 1710 cm^{-1} (keto-carbonyl). The n.m.r. spectrum had bands at τ 7.90 (singlet, $-\overset{O}{\overset{\|}{C}}-CH_3$) and τ 6.60 (broad, $-CH_2-$).

Treatment of the chloro compound with 2,4-dinitrophenylhydrazine in acetic acid under conditions to be outlined below yielded deep red crystals of melting point 204-205° after recrystallization from ethanol-chloroform. The ultraviolet spectrum of this derivative displayed intense absorption at 374 mμ.

12. Preparation of 2,4-Dinitrophenylhydrazones of LXXIX and LXXXI

Compound LXXIX (or LXXXI) (0.025 gm) was dissolved in glacial acetic acid containing 2,4-dinitrophenylhydrazine. The deep red solution was heated, with stirring, to 80° and maintained at that temperature for 18 hours. At the end of this period, the reaction was diluted with water, precipitating a red solid, m.p. 171-181°. After several recrystallizations from ethanol-chloroform, the melting

point was raised to a constant 204-205°C. The infrared spectrum in nujol mull (Figure 1) displayed prominent bands at 3290, 1630, 1615, 1590 cm^{-1}. The derivative displayed ultraviolet absorption at 374 mμ in ethanol solution.

13. Preparation of N-Chloro-N-methyl-acetamide (LXXXIII)

N-methylacetamide LXXXII (1 gm, 0.014 mole) was dissolved in carbon tetrachloride (25 mls) and a solution of sulphuryl chloride (1.8 gms, 0.014 mole) in carbon tetrachloride (10 mls) was added dropwise with stirring over a period of one hour. The colourless reaction solution was then stirred at room temperature for an additional 16 hours. At the end of this period an oil had precipitated. On separation of the carbon tetrachloride there was obtained a white semi-solid (1.4 gms) giving a positive Beilstein test. This material was subjected to vacuum sublimation (50° at 0.1 mm) to give transparent cubical crystals (1.35 gm, 92% yield) m.p. 85-87°. The infrared spectrum of this material displayed few bands, the most prominent being at 1610 (broad and weak) and 1450 cm^{-1}(medium). The compound LXXXII on the other hand displayed the correct secondary amide bands at 3290, 3090, 1650, 1560 and 1295 cm^{-1}. The n.m.r. spectrum of LXXXIII displayed two bands of equal area at τ 7.47 (singlet, $-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$) and τ 6.99 (singlet, $\underline{CH_3}-\overset{Cl}{\overset{|}{N}}-$).

14. The Preparation of 1,2,3,4-Tetrahydro-6-methoxyquinoline (XCIII)

6-Methoxyquinoline XCII, (50 gms, 0.31 mole) was dissolved in methanol (200 mls), to which was added platinum oxide (Adams' catalyst, 5 gms). The resulting suspension was hydrogenated at 50 psi in a Parr Hydrogenator. After 22 hours, uptake of hydrogen had ceased, and the catalyst, now granular, was removed by filtration. Evaporation of the solvent at the water aspirator yielded a light yellow oil (50.1 gm, 99%). Distillation of a small amount of this oil in vacuo produced a colourless liquid (b.p. 101-102°/0.5 mm) which slowly crystallized. The n.m.r. spectrum displayed the spectral characteristics listed in Table 1. Remeasuring the n.m.r. spectrum in the presence of deuterium oxide caused the disappearance of the band at τ 6.53, permitting its assignment to the -N-H group.

15. The Preparation of 9-Methoxyjulolidine (XXVIII)

1,2,3,4-Tetrahydro-6-methoxyquinoline XCIII (50 gm, 0.31 mole) was dissolved in 1-bromo-3-chloropropane (250 gm, 1.6 moles) and refluxed for 16-20 hours. The condenser was fitted with a rubber tube to lead off gases which form during the reaction. This tube led to a saturated aqueous solution of sodium carbonate, or better, was vented out a nearby window. At the end of the reflux period much solid had separated. The infrared spectrum of a small amount of these crystals showed them to be the mixed hydrochloride

and hydrobromide salts of XXVIII by broad absorption in the region 2700-2300 cm^{-1}. These salts were not isolated. The entire reaction mixture, including the solid, was diluted with hydrochloric acid (10%, 250 mls), and distilled water (1000 mls). The resulting dark-coloured suspension was distilled in order to steam-distil the unreacted 1-bromo-3-chloropropane. This latter material could be reclaimed by separation of the co-distilled water, drying, and redistilling. It could then be reused in this reaction.

The aqueous acidic residue from the steam-distillation was cooled to room temperature, basified to approximately pH 9 with concentrated ammonium hydroxide and extracted with several portions of petroleum ether (total volume of extract was 4-6 litres). It is recommended that a light hydrocarbon solvent be used for this extraction. The product XXVIII is unstable in the common chlorinated solvents, and the use of diethyl ether causes the extraction of much coloured material from the basic aqueous mixture. The petroleum ether extract was then dried over magnesium sulphate and distilled, using a Weston double surface condenser, which is well suited for the rapid distillation of large volumes of low boiling solvents. In this manner a light brown oil (45.5 gm, 74%) was obtained. The infrared spectral characteristics (carbon tetrachloride solution) of this oil, unchanged on vacuum distillation (b.p. 125-127°/ 0.18 mm), are: 1605, 1490, 1470, 845 cm^{-1}. The n.m.r. spectrum (carbon tetrachloride solution) of XXXIV is given in Figure 11.

Analysis. Calculated for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89%. Found: C, 76.54, 76.61; H, 8.23, 8.29; N, 6.84%.

The perchlorate salt of XXVIII was prepared by acidifying an ethereal solution of XXVIII with a reagent composed of ethanol-perchloric acid (1:1 v/v) and separating the crystals by filtration. These crystals (m.p. 186-187° after recrystallization from ethyl acetate-methanol) displayed infrared absorption (nujol mull) at 3030, 1600, 1590, 1100 cm^{-1}. The hydrochloride salt was also prepared by treating an ethereal solution of XXVIII with hydrogen chloride gas, and separating the crystals by filtration. These crystals (m.p. 185-188° after several recrystallizations from acetone) displayed infrared absorption (nujol mull) at 2250, 1595 cm^{-1}.

16. The Preparation of 1,2,3,4-Tetrahydro-6-hydroxyquinoline (XCIV)

1,2,3,4-Tetrahydro-6-methoxyquinoline XCIII (36 gms, 0.22 mole) was dissolved in hydrobromic acid (47%, 150 mls, redistilled b.p. 125°) and refluxed under a blanket of purified nitrogen for 6 hours. The reaction was then cooled and the precipitated solid collected by suction filtration. The crystals thus obtained were thoroughly washed with acetone, and dried in vacuo to yield 49.1 gms (97%) of light brown granular crystals (m.p. 153-154°). The infrared spectrum (nujol mull) of this material displayed absorption at 3240 cm^{-1}, 2740 cm^{-1} (broad),

1600 cm^{-1}.

The crystalline hydrobromide (2.79 gms, 0.01 mole) was dissolved in aqueous ethanol and basified with saturated aqueous sodium carbonate solution. This basic solution was extracted with several portions of ether which were combined, dried over magnesium sulphate, and evaporated. In this way a white powder (1.5 gm, 84%) was obtained (m.p. 147-149° on recrystallization from ethanol, literature (54) melting point 148°). The spectral characteristics of the crystalline amino-phenol are: infrared (nujol mull) 3290, 1490, 889 cm^{-1}; n.m.r. spectrum in trifluoroacetic acid: τ 8.1 (2H, multiplet), τ 7.38 (2, triplet, J=6 cps), τ 6.61 (2H, multiplet), τ 3.25 (3H, multiplet), τ 1.58 (2.5H, singlet).

17. The Preparation of 9-Hydroxyjulolidine (XCV)

1,2,3,4-Tetrahydro-6-hydroxyquinoline XCIV (9 gm, 0.06 mole) was suspended in 1-bromo-3-chloropropane (50 gm, 0.32 mole) in which it was not entirely soluble and refluxed under a blanket of purified nitrogen for 18 hours, with the usual provision for venting acid gases. At the end of this period much solid had separated, and was isolated from the cooled reaction mixture by suction filtration. The crystals were pulverized in a mortar and washed with acetone until the washings were colourless. In this way a light brown solid (5 gms) was obtained. The n.m.r. spectrum of this solid indicated a mixture composed of approximately 40 parts starting material and 60 parts reaction product. The solid

(5 gms) was dissolved in aqueous ethanol and basified with solid sodium bicarbonate. The dark coloured basic solution was extracted with several portions of ether, which were combined, dried, and evaporated to yield an amorphous solid (3.9 gms). Thin layer chromatography of this solid on alumina (sprayed with Dragendorffs' reagent (65)) indicated the presence of two components in about equal amounts. This material was dissolved in the minimum amount of ethanol, and diluted with anhydrous ether until the solution was just turbid. The solution was clarified by the addition of a few further drops of ethanol and acidified with a solution of perchloric acid in ethanol (1:1 v/v). The resultant mixture was filtered by suction to yield, after washing with acetone, a light brown crystalline solid (3.28 gms). Based upon the n.m.r. calculations which suggest the original reaction mixture is composed of 60% reaction product, the yield of perchlorate salt represents a 92% recovery of this component. The infrared spectrum (nujol mull) of the 9-hydroxy-julolidine perchlorate thus obtained displayed prominent bands at 3410, 3090, 1595, 1060 cm^{-1}; the n.m.r. spectrum in trifluoroacetic acid solution is given in Figure 12.

Conversion of a small amount of the perchlorate to the corresponding base XCV by treating an ethanol-water solution of the salt with saturated aqueous sodium bicarbonate followed by the usual work-up yielded the amino-phenol XCV as a white powder. The n.m.r. spectrum of XCV in trifluoroacetic acid is superimposable on that of the perchlorate derivative determined in the same solvent.

18. The Preparation of 9-Methoxy-8,10a-dihydrojulolidine (XXXVI)

9-Methoxyjulolidine XXVIII (41 gms, 0.2 mole) in ether (100 mls) was dissolved in liquid ammonia (1500 mls, redistilled) contained in a three litre, three necked, round-bottomed flask fitted with a dry-ice condenser and a powerful mechanical stirrer. To the rapidly stirred colourless solution was added metallic lithium (12 gms, 0.87 mole) cut in small pieces. The rapid addition of t-butanol (300 mls) in ether(100 mls) was commenced immediately and carried out as quickly as possible (15-20 minutes). Solid granular ammonium chloride was then added until the excess lithium had been destroyed as judged by the disappearance of the characteristic blue colour of the lithium-ammonia solution. It was felt important to keep the time of exposure of XXVIII to metallic lithium as short as possible and hence it is recommended that this reaction be carried out as rapidly as possible. The liquid ammonia was then evaporated in a rapid stream of nitrogen and the white to brown residue taken up in distilled water (1000 mls). This basic aqueous solution was extracted with several portions of ether which were combined, dried over magnesium sulphate, and evaporated to yield an amber oil (41 gms). The success of the reaction was monitored at this point by the measurement of the n.m.r. spectrum of a small quantity (0.1 gm) of the oil. As a general rule this showed maxima, in carbon tetrachloride solution at τ 8.8 (associated with t-butanol), 8.15 (broad envelope), 7.25 (broad envelope), 6.52, and

5.5. In this case, the reaction was complete, since the band at τ 6.42 in the spectrum of XXVIII was absent in this spectrum. Thus the remainder of the product was without further purification or characterization converted to the ethylenedioxy iminium-perchlorate.

During the development of conditions for this reaction, occasion was had to convert some of XXXVI to its perchlorate derivative by the following procedure. 9-Methoxy-8,10a-dihydrojulolidine XXXVI (0.10 gm, 4.9 x 10^{-4} mole) was dissolved in anhydrous ether (10 mls) and acidified with perchloric acid-ethanol solution (1:1 v/v). The precipitated solid was collected by suction filtration and washed well with ether. In this way an off-white crystalline solid (0.14 gm, 94%) was obtained. The infrared spectrum of this perchlorate (nujol mull) displayed bands at 1670 and 1085 cm^{-1}.

19. The Preparation of 9-Methoxy-7a,8,10a,11-tetrahydrojulolidine (XCVI)

9-Methoxyjulolidine XXVIII (10 gms, 0.049 mole) was dissolved in ether (50 mls) and the clear solution was added to liquid ammonia (1500 mls, redistilled) contained in the apparatus outlined in experiment 18. Metallic lithium (5.2 gms, 0.74 mole) was added piecewise to the rapidly stirred solution. Stirring was continued for 30 minutes, at the end of which time ethanol was added dropwise until the blue colour of the lithium-ammonia solution was discharged. The ammonia was allowed to evaporate at

room temperature overnight. The solid residue was taken up in distilled water (ca 200 mls) and extracted with several volumes of dichloromethane, which upon drying and evaporating yielded a dark-brown mobile oil (10 gms). The n.m.r. spectrum of this product (determined in carbon tetrachloride solution) showed bands at τ 6.38 associated with the aromatic methoxyl protons of XXVIII and at τ 6.58, associated with the methoxyl protons of the enol ether group of XCVI. Relative integral intensities indicated 54% reduction. Attempts to separate this mixture by column chromatography on neutral alumina were unsuccessful. Separation was effected by distilling the oil (4.7 gms) in vacuo in a short-path "collar flask." In this way a colourless oil (1.85 gms, b.p. 71°/ 0.07 mm) was obtained, whose n.m.r. spectrum displayed resonance maxima at τ 7.5-9.5 (broad envelope), 7.3 (unresolved multiplet), 6.58 (3H, sharp singlet), and 5.82 (1H, singlet). There was no resonance in the aromatic proton region. This separation of XCVI thus represents a 74% recovery of the total reduced material. The structure XCVI was assigned on the basis of the n.m.r. spectrum and the mass spectrum (Figure 24) of the distilled substance, which showed a parent peak at m/e 207 and an intense peak at 192 (M-15).

20. <u>The Preparation of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine Perchlorate (XCVIII)</u>

9-Methoxy-8,10a-dihydrojulolidine XXXVI (41 gms, 0.2 mole) was slowly added by means of a hypodermic syringe fitted with an 8 inch needle to a rapidly stirred solution

of 70% perchloric acid (100 mls) in ethylene glycol (1000 mls). A thick precipitate soon appeared. The viscous mixture was stirred for 12-16 hours and the precipitate separated by suction filtration. The filter cake was then digested in boiling methanol (200 mls) for one hour and refiltered to yield a white powder (46 gms, 75%). Recrystallization of a portion of this material from acetone gave colourless needles, m.p. 258-259° dec. The infrared spectrum of the perchlorate showed bands at 1680 and 1085 cm^{-1}.

Analysis: Calculated for $C_{14}H_{22}O_6NCl$: C, 50.05; H, 6.60; N, 4.17%. Found: C, 50.51, 50.44; H, 6.57, 6.63; N, 4.00%.

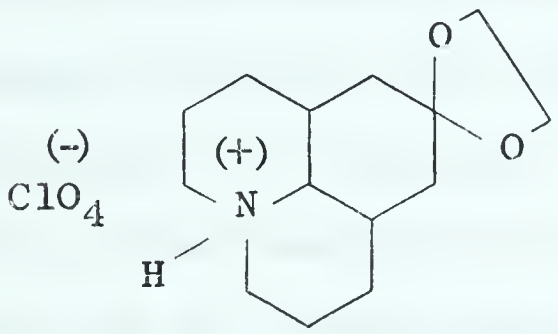
A small portion of the iminium perchlorate was converted to the free base XCIX in the usual way to yield a colourless oil, whose infrared spectrum (chloroform solution) displayed a prominent band at 1645 cm^{-1}; and whose n.m.r. spectrum in carbon tetrachloride solution is given in Figure 13.

21. Preparation of the Ethylenethioketal CLI of 9-Keto-7a,8,9,10,10a,11-hexahydrojulolidine

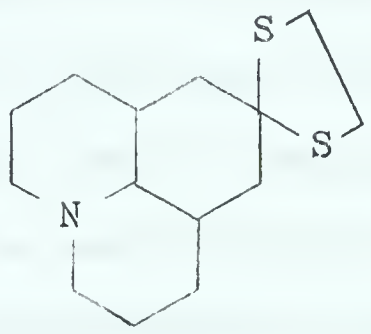
(a) The Catalytic Reduction of 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine Perchlorate (XCVIII).

Compound XCVIII (0.5 gm, 1.7×10^{-3} mole) was suspended in methanol (50 mls) to which had been added Adams' catalyst (0.15 gm) and hydrogenated at atmospheric pressure. Uptake of the gas was complete after 90 minutes.

The solvent was filtered free of the spent catalyst and evaporated at the water pump to yield a brownish oily solid (0.550 gm). Trituration of this material with ethyl acetate yielded a light brown powder (0.356 gm, 71%) whose infrared spectrum (nujol mull) shows absorption at 3090 cm^{-1} ($-\overset{|}{\underset{|}{N}}\overset{(+)}{-}H$) and 1050 cm^{-1} ($\overset{(-)}{ClO_4}$). There was no absorption attributable to an olefinic linkage. Structure CLII is assigned to this substance.



CLII



CLI

A portion of CLII was converted to the corresponding CLIII by dissolving it in methanol-water, and basifying with saturated aqueous sodium carbonate. The aqueous suspension was extracted with several portions of petroleum ether, which on drying and evaporating yielded a white crystalline solid (m.p. 161-164°). The n.m.r. spectrum of this solid (carbon tetrachloride solution) displayed bands at τ 8.0-9.0 (broad envelope), 7.3 (poorly resolved multiplet), and 6.15 (4H, sharp singlet).

(b) <u>The Reaction of CLII with Ethanedithiol</u>

The ethylene ketal perchlorate CLII (0.145 gm, 4.75×10^{-4} mole) was dissolved in hot acetic acid (10 mls)

to which was added ethanedithiol (1 ml) and boron trifluoride etherate (1 ml). The clear solution was allowed to stand with occasional shaking for 3 hours. At the end of this period, the acetic acid was neutralized with dilute ammonium hydroxide and the basic solution extracted with several portions of petroleum ether. Evaporation of the dried solvent yielded a white odorless solid (0.068 gm, 53%, m.p. 138-140°). The n.m.r. spectrum of this solid (carbon tetrachloride solution) showed a band at τ 6.77 whose relative integral intensity was nearly 4/22 of the total intensity (allowance for background being made) and no resonance at τ6.15. The remainder of the spectrum was virtually identical with that of the base CLIII. The mass spectrum (Figure 22) of the thioketal showed a parent peak at m/e 269, and none at m/e 237, making the assignment of structure CLI to it possible.

22. The Preparation of 9-Ethylenedioxy-11-allyl-7a,8,9,10,10a-hexahydrojulolidine (CV)

Magnesium metal (0.3 gm, 0.012 mole) was added to a solution of allyl bromide (0.7 ml, 0.01 mole) in refluxing tetrahydrofuran (200 mls, anhydrous, distilled from lithium aluminium hydride) contained in a three-necked round-bottom flask (500 mls) equipped with a reflux condenser, gas addition tube, and a magnetic stirrer. The reaction mixture was protected from moisture and atmospheric oxygen by calcium sulphate drying tubes and a blanket of purified oxygen free (66) nitrogen and maintained at

reflux for 24 hours. At the end of this time most of the magnesium had dissolved, the remainder having become coated with a black film. 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine perchlorate XCVIII (1.78 gm, 5.3 x 10^{-3} mole) which had been finely divided by crushing in a mortar, was added to the hot solution of allyl magnesium bromide in one portion and the solution maintained at 63^{o} for 24 hours. The colourless reaction was then allowed to cool and distilled water (50 mls) added dropwise to decompose the Grignard complex. This addition was accompanied by much foaming. The aqueous solution was basified with concentrated ammonium hydroxide and extracted with petroleum ether. Drying this solvent over magnesium sulphate and evaporating it in vacuo yielded a light brown oil (1.34 gm). Thin layer chromatography indicated the presence of two components, one of which was starting material XCIX.

The reaction product (1.34 gm) was added to a stirred solution of 70% perchloric acid (10 mls) in ethylene glycol (100 mls). A solid precipitate appeared immediately, and the reaction was allowed to stir at room temperature for 16 hours. Collection of the precipitate by suction filtration and drying it in vacuo at 65^{o} provided 0.49 gm of white crystals, whose infrared spectrum displayed bands at 1678 cm^{-1}, and 1085 cm^{-1}. Comparison of this spectrum with that of authentic starting material revealed their identity.

The ethylene glycol filtrate from above was diluted with distilled water (250 mls), and basified with

saturated aqueous sodium carbonate. Extraction of this basic solution with petroleum ether, drying the extract over magnesium sulphate, and evaporating it yielded a brown oil (0.91 gm). Thin layer chromatography of this oil revealed the presence of two components, neither of which was starting material, and one of which was identical to the second component of the crude Grignard reaction product. This new mixture is thus suggested to contain CV and CVI.

The mixture (0.91 gm) of CV and CVI was dissolved in benzene (150 ml) contained in a round-bottomed flask equipped with a Dean-Stark water separator. To this solution were added ethylene glycol (0.4 ml) and paratoluenesulphonic acid (2.0 gms, 0.01 mole) and the mixture refluxed for 20 hours. The clear reaction solution was then washed with saturated aqueous sodium carbonate until the washings were basic to litmus paper. Drying the organic layer with anhydrous magnesium sulphate and evaporating it at the water aspirator yielded a brown oil (0.89 gm) which slowly crystallized. The infrared spectrum of these crystals in carbon tetrachloride displayed maxima at 3080 cm^{-1}; 2870, 2815, 2780, 2759, 2680 cm^{-1}; 1632 cm^{-1}. Sublimation of a small amount of this substance, now identified as CV, at 0.07 mm and 70° yielded large colourless cubical crystals, m.p. 107°. The infrared spectrum (nujol mull) of this sublimate CV is shown in Figure 4, the n.m.r. spectrum in Figure 14.

The mass spectrum of the sublimate (Figure 28), while not displaying a parent peak at m/e 277, does contain

a peak at m/e 236 as well as several others which are interpreted in terms of CV. Thus this structure is assigned to the crystalline sublimate.

23. The Preparation of 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine (CVIII)

(a) The reaction in diethyl ether

An apparatus was assembled consisting of one litre three-necked round-bottomed flask equipped with two reflux condensers, calcium sulphate drying tubes, a gas inlet tube, and a magnetic stirring bar. A stream of oxygen-free purified nitrogen (66) was passed into the apparatus, the flask was flame-dried and allowed to cool. Diethyl ether (500 mls) which had been dried by refluxing for 4 hours over excess lithium aluminium hydride, was distilled from that reagent into the dried flask. Metallic magnesium (1.4 gm, 0.058 mole) was added, stirring begun, and the ether heated to reflux. Methallyl chloride (5.4 gms, 0.06 mole) in anhydrous ether (50 mls) was added in three portions over a period of one hour to the refluxing reaction. Turbidity appeared almost at once. After stirring and refluxing for 24 hours additional methallyl chloride (2.0 gm, 0.02 mole) was added, and refluxing continued for a total of 60 hours.

9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine perchlorate XCVIII (9.7 gms, 0.03 mole) was then rapidly added to the ethereal reaction mixture, accompanied by much foaming. After refluxing for 48 hours, an aliquot

(2 mls) was withdrawn, diluted with water (25 mls) and extracted with ether. The extracts were combined, dried, and evaporated to yield a colourless oil (0.037 gm). The infrared spectrum (thin film) of this oil indicated by the presence of absorption at 3070 and 1630 cm^{-1} the likely presence of CVIII in the aliquot. Reflux was continued for a further 48 hours, at which time a second aliquot (5 mls) was removed and worked-up as before to yield a colourless oil (0.063 gm). The n.m.r. spectrum of this oil in chloroform displayed bands attributable to olefinic proton resonance at τ 5.2 as a broad poorly resolved envelope, and to the ethylenedioxy protons at τ 6.08 as a sharp singlet. The relative integral ratios of these two bands show that approximately 50% of the material containing the ethylenedioxy group also contains the olefinic protons. The reflux was allowed to proceed for an additional 48 hours, when a third aliquot (5 mls) was removed and worked-up as before to yield a colourless oil (0.069 gm). The n.m.r. spectrum of this oil contained the same bands as did that of the second aliquot, but in this case the band attributed to the olefinic protons was centered at τ 5.14 (splitting 5 cps). The relative integral ratios of the two relevant bands indicate that almost 100% of the material containing the ethylenedioxy group contains olefinic protons. The reaction thus appeared to be almost complete, and was allowed to reflux another 24 hours. Again an aliquot (5 mls) was removed and worked-up to yield a colourless oil (0.061 gm) which was converted to its perchlorate derivative in the

usual way to yield light-brown sugary crystals (0.074 gm, 94%). The infrared spectrum of this perchlorate (nujol mull) displayed absorption at 3105 cm^{-1}, 1638 cm^{-1}, and 1105 cm^{-1}. There was no absorption in the region 1650-1750 cm^{-1}.

Since the n.m.r. spectrum of the third aliquot and the infrared spectrum of the perchlorate of the fourth provided ample evidence the reaction was complete, the main reaction was worked-up as follows. The ethereal suspension was allowed to cool and distilled water (200 mls) was added dropwise with vigorous stirring, which was continued for 1 hour after the addition was complete. The ethereal layer was separated and the aqueous layer extracted with several portions of ether, which were combined with the original ethereal layer, dried over magnesium sulphate, and evaporated. In this way it was possible to obtain a brown oil (7.46 gms, 89%) which was converted in the usual way to its perchlorate derivative to yield light brown crystals (7.72 gm, 77%), whose infrared spectrum was identical with that of the perchlorate obtained from the fourth aliquot.

CVIII as prepared in this way was not subjected to elementary analysis.

(b) The reaction in tetrahydrofuran

This reaction was conducted using the same apparatus as was used when diethyl ether was the solvent, and was carried out under oxygen-free nitrogen.

Tetrahydrofuran (1000 mls) which had previously been dried by refluxing over lithium aluminium hydride for

four hours was distilled into the reaction vessel. Metallic magnesium (3.1 gms, 0.13 mole) was added, stirring begun, and the tetrahydrofuran brought to reflux. Methallyl chloride (12 gms, 0.13 mole) in tetrahydrofuran (50 mls) was added dropwise to the refluxing mixture. The reaction became discoloured almost at once and was allowed to continue refluxing for 14 hours. 9-Ethylenedioxy-8,9,10,10a-tetrahydrojulolidine perchlorate XCVIII (20 gms, 0.06 mole) which had been finely ground in a mortar, was then added in one portion, the addition being accompanied by much foaming. The mixture was refluxed for one hour, at which time an aliquot (5 mls) was removed and worked-up as described in procedure 23(a). The oil which was obtained in this way was converted to the perchlorate derivative as usual to yield white crystals. The infrared spectrum of these crystals (nujol mull) displayed bands at 3105 cm^{-1}, 1638 cm^{-1}, and 1100 cm^{-1}. There was no absorption in the region 1650-1750 cm^{-1}. Since it was thus indicated that the reaction was complete, distilled water (300 mls) was added slowly to the hot reaction mixture. The aqueous solution was extracted with several portions of ether, which were combined, dried over magnesium sulphate, and evaporated to yield a murky red oil. This oil was treated again with ether (500 mls) and the resulting red suspension filtered to remove a small amount of ether-insoluble gum. Redrying the filtrate and evaporating it gave an orange oil (12.8 gms, 74%). The infrared spectrum of CVIII thus prepared displayed bands at 3078 cm^{-1}; 2897, 2872, 2812, 2780, 2756, 2685 cm^{-1}; 1631 cm^{-1}. Thin

layer chromatography showed the presence of two components in CVIII, the less polar the minor, the more polar the major, these being the stereoisomers CX and CXI.

This mixture CVIII (1.0 gm) was subjected to column chromatography over alumina (neutral Woelm, Brockmann number 1). The progress of the chromatogram was monitored by thin layer chromatography, and the results are indicated in Table 4. The infrared spectrum of fraction 2

Table 4

Column Chromatography of CVIII

Fraction	Eluent	Yield gm.	Number of Components
1	100% Benzene	-	-
2	1:9 Ether/Benzene	0.548	2
3	1:9 Ether/Benzene	0.382	1

(a new mixture in which the components are now present in about equal amounts) in carbon tetrachloride is identical with that of CVIII before chromatography. The spectrum of fraction 3 (the separated portion of the more polar major component of CVIII) in carbon tetrachloride displayed bands at 3082 cm^{-1}; 2900, 2878, 2817, 2785, 2762, 2707, 2691 cm^{-1}; 1636 cm^{-1}. The fingerprint region (1000-1500 cm^{-1}) of this spectrum was virtually superimposable on that of both fraction 2, and unchromatographed CVIII, differing only in that the bands in the spectrum of fraction 3 are sharper than the others. Fraction 3, identified as CXI, slowly

crystallized to form a low melting (54-56°) solid.

Analysis: (Fraction 3, CXI) The sample was prepared for analysis by consecutive sublimations at 70°/0.1 mm, 130°/1 mm, and 152°/2.5 mm. Calculated for $C_{18}H_{29}O_2N$: C, 74.17; H, 10.04; N, 4.81%. Found: C, 73.92, 74.27; H, 9.85, 9.78; N, 4.89%.

The n.m.r. spectrum of CVIII (unchromatographed) is given in Figures 15, 16. The n.m.r. spectrum of CXI (fraction 3) is given in Figure 17.

The perchlorate derivative of a small amount of fraction 3 (Table 4) was prepared as usual. White crystals (m.p. 247-249° dec.) were obtained after two recrystallizations from methanol. The infrared spectrum of this derivative (nujol mull) displayed bands at 3104 cm^{-1}; 1536 cm^{-1}; 1100 cm^{-1}. The remainder of the spectrum was very similar to that of unchromatographed CVIII and fraction 2 (Table 4).

24. The Reaction of 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CXI with Methyl Iodide in Various Solvents

9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a-hexahydrojulolidine CXI (0.025 gm, 8.6 x 10^{-5} mole) was added to a solution of methanol (0.15 ml, 1%) in anhydrous ether (15 mls). Methyl iodide (0.15 ml, 1%) was then added and the colourless solution refluxed for one hour. At the end of this time, the solvents were evaporated to yield a colourless oil (0.024 gm) which soon crystallized. Thin

layer chromatography of the crystals showed them to be starting material.

The experiment was repeated without methiodide formation in solvents containing the following percentages of methanol: 0, 1, 2, 5, 7, 10, 15.

Carrying the experiment out in solvent containing 17% methanol produced a brown oil (0.023 gm) which contained two components, as disclosed by thin layer chromatography. One component was identified as CXI; the other, much more polar, as the corresponding methiodide.

(b) The Reaction of 11-Methallyl-7a,8,9,10, 10a,11-hexahydrojulolidine XLII (R=methallyl) with Methyl Iodide in Various Solvents

The procedure and results of this experiment are identical to those reported in experiment 24(a).

25. The Ozonation of 11-Methallyl-7a,8,9,10, 10a,11-hexahydrojulolidine XLII[1] (R=Methallyl)

11-Methallyl-7a,8,9,10,10a,11-hexahydrojulolidine XLII (R=methallyl) (0.56 gm, 0.002 mole) was dissolved in ethyl acetate (50 mls) cooled to Dry-Ice temperatures and treated with ozone produced by a Welsbach Ozonator operated under the following conditions: air supply 7.5 psi, generator voltage 90 v, flow rate of ozone/air to reaction vessel 0.03 cfm. Ozonation was continued until the characteristic blue colour of ozone dissolved in cold ethyl acetate appeared (1-1/2 hours).

This crude reaction mixture was subjected to catalytic hydrogenation at 15 psi over palladium carbonate/

[1]Compound XLII was prepared By J.A.C. Soper (57).

charcoal for 4 hours. At the end of this period the catalyst was removed by filtration and the ethyl acetate solvent removed in vacuo, to yield a yellow oil with a very pungent odour. This oil was redissolved in ethyl acetate and washed with saturated aqueous sodium carbonate until the washings were basic. The organic solution was then dried over anhydrous sodium sulphate and the solvent evaporated to yield an odourless yellow oil (0.62 gm, 100%). The infrared spectrum of this oil (as a thin film) displayed bands at 3400, 1700, 1650 cm^{-1}.

26. The Preparation of 11-[2-Ketopropyl]-7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate (CXXII)

11-Methallyl-7a,8,9,10,10a,11-hexahydrojulolidine XLII (R=methallyl) as its perchlorate derivative (11.9 gms, 0.036 mole) was dissolved in ethanol (350 mls), cooled to -10^{o} in Dry-Ice, and treated with ozone produced under the same conditions as outlined in experiment 25. Ozonation was continued for 90 minutes.

The crude reaction mixture was subjected to catalytic hydrogenation at 30 psi over palladium carbonate/charcoal for 3 hours. The catalyst was removed by suction filtration and the colourless filtrate concentrated in vacuo to yield white cubical crystals (8.96 gms, 76%), m.p. 188-189^{o}, whose infrared spectrum in nujol (Figure 5), displayed absorption at 3122 cm^{-1}, 1704 cm^{-1}, 1420 cm^{-1}, and 1095 cm^{-1}. Further concentration yielded a crop of white needles (m.p. 200-215^{o}) whose infrared spectrum

demonstrated bands at 3115 cm^{-1}, 1704 cm^{-1}, 1670 cm^{-1} and 1095 cm^{-1}, identified as a mixture of the desired ketone and the iminium perchlorate CXIX.

Recrystallization of the main product (8.9 gms) from ethanol yielded shining white needles (4.35 gms, 60%), m.p. 206-207°, whose infrared spectrum displayed bands at 3115 cm^{-1} (weak), 1665 cm^{-1}, 1085 cm^{-1}. It was thus identified as perchlorate CXIX.

The iminium perchlorate CXIX (1.0 gm, 0.0044 mole) was dissolved in ethanol/water, and the resulting solution basified with saturated aqueous sodium carbonate. Work-up as usual yielded a colourless oil (0.346 gm, 55%) whose infrared spectrum displayed absorption at 2860, 2822, 2800, 2762, 2670 cm^{-1}; 1630 cm^{-1}, permitting its identification as enamine XXXVII. The oil was converted to its perchlorate derivative in the usual way to yield white crystals, whose infrared spectrum in a nujol mull exhibited bands at 3110 cm^{-1} (weak); 1662 cm^{-1}; 1625 cm^{-1} (very weak); 1080 cm^{-1}, identical with the product of crystallization from ethanol above (m.p. 206-207°).

27. The Preparation of 9-Ethylenedioxy-11-[2-ketopropyl]-7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate CXXIII

9-Ethlenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine CVIII as its perchlorate derivative (5.0 gms, 0.013 mole) was dissolved in a solution of ethanol-ethyl acetate (300 mls, 2:1 v/v), cooled to -50° by means of a Dry-Ice bath and treated with ozone produced

under the same conditions as outlined in experiment 25. Ozonation was continued for 3 hours.

This crude reaction mixture was subjected to catalytic hydrogenation at 35 psi over palladium carbonate/charcoal for 24 hours. At the end of this time sugary crystals had separated from the reduction solution. The catalyst, as well as the crystals, was separated by filtration. The filter cake was washed repeatedly with portions of boiling ethanol until the crystals had been leached out of the catalyst. The washings were combined with the original filtrate and the whole diluted with several volumes of ether to precipitate white cubical crystals (1.498 gms, 34%). The infrared spectrum in a nujol mull (Figure 6) of CXXIII (m.p. 271-272^{o} after several recrystallizations from ethanol) thus prepared displayed absorption at 3120 cm^{-1}; 1695 cm^{-1}; 1445 cm^{-1}; 1060 cm^{-1}.

The ethereal filtrate (25 mls) was treated with a saturated solution of 1,3-diketo-5,5-dimethylcyclohexane (dimedone) in ethanol (5 mls). The solution was evaporated to a small volume (ca 5 mls) and cooled overnight in a refrigerator. This caused the precipitation of a white solid, which was separated by suction filtration to yield pure white crystals (m.p. 194-195^{o}, mmp. 195-196^{o} with authentic dimedone derivative of formaldehyde).

CXXIII (0.061 gm, 1.6 x 10^{-4} mole) was dissolved in water (10 mls) and ethanol added to the point of incipient turbidity. The solution was then basified by the addition of saturated aqueous sodium carbonate. The basic

aqueous suspension was extracted with several portions of ether, which were combined, dried, and evaporated to yield a light brown oil (0.023 gm, 84%). The infrared spectrum of this oil displayed bands at 1700 (cyclohexanone-carbonyl), 1690 (2-ketopropyl carbonyl), and 1640 cm^{-1} (enamine, from loss of the C-11 substituent).

28. Photolysis of 9-Ethylenedioxy-11-[2-ketopropyl]-7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate CXXIII in Aqueous Solution

CXXIII (0.563 gm, 1.44×10^{-3} mole) was dissolved in distilled water (150 mls) from which dissolved oxygen had been expelled by boiling it for 30 minutes and allowing it to cool under a blanket of oxygen-free nitrogen. This solution was placed in a specially designed photolysis vessel containing a well for the source of the radiation and an annular space between the well and the reaction mixture through which coolant could be circulated in order to eliminate unwanted heating effects caused by the lamp. The vessel was also equipped with a gas inlet at the bottom in order that gases could be bubbled through the reaction as well as provision for a condenser to allow reactions to be carried out at elevated or reflux temperatures. The vessel was surrounded by a sheet of aluminium foil both to protect the eyes of observers and to reflect as much radiation as possible back into the reaction mixture. The photolysis was carried out using an Hanovia mercury arc for 6 hours. Cooling water was circulated at such a rate as to maintain the reaction solution at a temperature of 70-80°. The yellow aqueous solution was then

cooled, basified to pH 9 with saturated aqueous sodium carbonate, and extracted with several portions of chloroform. The extracts were combined, dried and evaporated to yield a yellow oil (0.338 gm, 60%) whose infrared spectrum in carbon tetrachloride displayed bands at 2880, 2855, 2828, 2800, 2765, 2675 cm^{-1}; 1710 cm^{-1}; 1640 cm^{-1}. There was no absorption in the region 3300-3100 cm^{-1}.

A small amount of this yellow oil was converted to its perchlorate derivative in the usual way to yield a white powder, which displayed infrared absorption (nujol mull) at 1715 cm^{-1} (weak), 1670 cm^{-1} and 1080 cm^{-1}.

29. Photolysis of 9-Ethylenedioxy-11-[2-ketopropyl] -7a,8,9,10,10a,11-hexahydrojulolidine Perchlorate CXXIII in Acetonitrile

Acetonitrile (550 mls) was refluxed over phosphorous pentoxide (25 gms) for 20 minutes and then fractionated through a 2 foot Vigreaux column. The first 50 and the last 100 millilitres of the liquid were rejected.

CXXIII(0.5 gm, 0.0013 mole) was dissolved in acetonitrile (300 mls), purified as above, and placed in the photolysis apparatus. The colourless solution was photolysed at room temperature for 48 hours. At the end of this period, the acetonitrile was removed by evaporation in vacuo and the resulting yellow oil triturated with ethanol. In this way light brown crystals (0.371 gm, 88%) were obtained. The infrared spectrum (nujol mull) of these crystals displayed absorption at 1675 cm^{-1}, 1080 cm^{-1}. The spectrum was

essentially superimposable on a spectrum of authentic XCVIII, thus identifying the reaction product.

30. The Photosensitized Oxidation of 9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine (CVIII)

(a) Methylene blue as photosensitizer

Compound CVIII (0.40 gm, 1.37×10^{-3} mole) and methylene blue (0.004 gm) were dissolved in 95% ethanol (50 mls). This solution was placed in a 25 mm vertical tube which was equipped with a cold-finger condenser. The reaction was irradiated from a distance of about 6 inches by a mercury arc lamp while a slow stream of oxygen was bubbled through. After a period of 17 hours, an aliquot (5 mls) was removed and warmed with a small amount of animal charcoal. Filtration of this charcoal suspension gave a colourless filtrate which, after evaporation of the solvent at room temperature in a stream of nitrogen, yielded a small amount of yellow oil. The infrared spectrum of this oil (carbon tetrachloride solution) displayed bands at 3080 cm^{-1} ($-\overset{|}{C}=CH_2$); 2875, 2765, 2680, 2660 cm^{-1} (Bohlmann bands); 1700, 1645 and 1630 cm^{-1}. After an additional 24 hours the entire reaction was worked-up in the same way as the aliquot above to yield a yellow oil (0.138 gm). The infrared spectrum of this material (carbon tetrachloride solution) displayed absorption at 3525 cm^{-1}; 3075 cm^{-1}; 2885, 2810, 2775, 2755, 2680 cm^{-1}; 1695 cm^{-1}; 1645 cm^{-1}. These data are interpreted in terms of structures LII and CXXXIV.

(b) Eosin yellow as photosensitizer

CVIII (0.50 gm, 1.72 x 10^{-3} mole) was subjected to the reaction described in experiment 30(a), using as the photosensitizing agent the dye eosin yellow. After irradiation for 72 hours work-up as described above gave unreacted CVIII (0.461 gm, 92%).

31. Preparation of 9-Keto-11-[1-(2-methyl-1-propenyl)]-7a,8,9,10,10a,11-hexahydrojulolidine (CXXXV)

9-Ethylenedioxy-11-methallyl-7a,8,9,10,10a,11-hexahydrojulolidine XLVIII (1.46 gms, 0.005 mole) was dissolved in 5% hydrochloric acid (100 mls) and refluxed for 77 hours. At the end of this time the reaction was allowed to cool, basified with a solution of saturated aqueous sodium carbonate and distilled water (1:1 v/v) and extracted with several portions of ether. The extracts were combined, dried with magnesium sulphate and evaporated, to yield a yellow oil (0.851 gm, 69%). Thin layer chromatography of this crude oil showed the presence of two components, both of slightly different R_f values than those of the starting material components. The infrared spectrum of CXXXV thus prepared (carbon tetrachloride solution) is reproduced in Figure 7; the n.m.r. spectrum (carbon tetrachloride solution) in Figure 18.

32. The Preparation of 9-Ethylenedioxy-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine (CXLV)

9-Ethylenedioxy-11-methallylhexahydrojulolidine CXI (1.1 gm, 3.8×10^{-3}) was dissolved in methanol (50 mls) to which was added Adams' catalyst (0.15 gm) and the mixture was hydrogenated in a Parr apparatus at 50 psi for 24 hours. At the end of this period, the spent catalyst was removed by filtration, and the solvent stripped at the water pump. By this method a light yellow oil (0.787, 72%), later a crystalline solid (m.p. 51-53°) was obtained. The infrared spectrum (Figure 8) of these crystals (in carbon tetrachloride) did not display any olefinic resonance. The mass spectrum of this product (Figure 26) while not displaying a parent peak at m/e 293 corresponding to CXLV may be interpreted in terms of this structure. Formula CXLV is thus assigned to this product on the basis of the spectral evidence and the mode of formation.

33. The Preparation of 9-Keto-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine (CXL)

Compound CXLV (0.474 gm, 1.6×10^{-3} mole) was dissolved in methanol (25 mls) to which was added distilled water (100 mls). Concentrated hydrochloric acid (25 mls) was then added and the resulting clear solution stirred at room temperature for 24 hours. At the end of this period the reaction was basified with saturated aqueous sodium carbonate and extracted with several portions of ether. Drying the solvent with anhydrous magnesium sulphate, and

evaporating it produced a pale yellow oil (0.343 gm, 86%) whose infrared spectrum (carbon tetrachloride solution, Figure 9) showed strong absorption at 1708 cm^{-1} (keto-carbonyl).

The hydrobromide salt of this product was prepared in the usual way to yield a light brown powder whose infrared spectrum (nujol mull) displayed intense absorption at 1695 cm^{-1} (keto-carbonyl) and broad absorption at 2700 cm^{-1} ($-\overset{|}{\underset{|}{N}}\overset{(+)}{-}H$). The perchlorate derivative was also prepared in the usual way and was obtained as a white crystalline solid (m.p. 268-270° dec.) whose infrared spectrum (nujol mull) displayed absorption at 3110 cm^{-1} ($-\overset{|}{\underset{|}{N}}\overset{(+)}{-}H$), 1698 cm^{-1} (keto-carbonyl), and 1075 cm^{-1} ($\overset{(-)}{ClO_4}$).

The mass spectrum of the product is shown in Figure 25 and supports the assignment of structure CXL to this material.

34. The Preparation of 8-Bromo-9-keto-11-isobutyl-7a,8,9,10,10a,11-hexahydrojulolidine (CXLVII)

Compound CXL (0.480 gm, 1.9×10^{-3} mole) was dissolved in chloroform (10 mls) which was acidified by the addition of a saturated solution of anhydrous hydrogen bromide in chloroform. Then bromine in chloroform (1.43 mls of a 6.1% solution of bromine in chloroform) was added dropwise from a one millilitre hypodermic syringe with stirring. The red bromine colour was rapidly discharged. The yellowish solution was then stirred at room temperature for 4 hours and shaken with saturated aqueous sodium

bicarbonate. The aqueous layer was separated and extracted with several portions of chloroform. The original chloroform layer was combined with the extracts, the whole dried with anhydrous magnesium sulphate and the solvent removed at the water pump. This procedure yielded a light yellow solid (0.532 gm, 84%) which gave a positive Beilstein test for halogen. The infrared spectrum (Figure 10) of this bromo-compound (in carbon tetrachloride) showed a maximum at 1730 cm^{-1} (equatorialα-halo-ketone) and no absorption between 1720 and 1600 cm^{-1}.

Attempts to purify his material by sublimation or column chromatography on neutral alumina resulted in extensive decomposition. Thin layer chromatography showed that the reaction product consisted essentially of one component, of greater polarity than the starting material.

Compound CXLVII (0.025 gm, 7.6×10^{-4} mole) was dissolved in glacial acetic acid (20 mls) to which was added 2,4-dinitrophenylhydrazine (0.016 gm, 8.1×10^{-4} mole). The resulting orange solution was maintained at 80° for 24 hours. At the end of this period the reaction was diluted with several volumes of water, basified with saturated aqueous sodium carbonate, and filtered. This method produced reddish orange powder in low yield. The ultraviolet spectrum of this hydrazone (in ethanol solution) displayed a very intense maximum at 372 mμ, as expected for α,β-unsaturated 2,4-dinitrophenylhydrazones, and structure CXLVIII is assigned to this product.

35. Preparation of 9-Keto-11-isobutyl-7a,8,9,10,10a,11 hexahydrojulolidine 2,4-dinitrophenylhydrazone CXLIX

CXLIX (0.020 gm, 8 x 10^{-5} mole) was treated with 2,4-dinitrophenylhydrazine under the same conditions as given in experiment 34. This procedure yielded a small amount of a reddish orange powder whose ultraviolet spectrum displayed a strong maximum at 361 mμ as expected for a saturated 2,4-dinitrophenylhydrazone. Structure CXLIX is accordingly assigned.

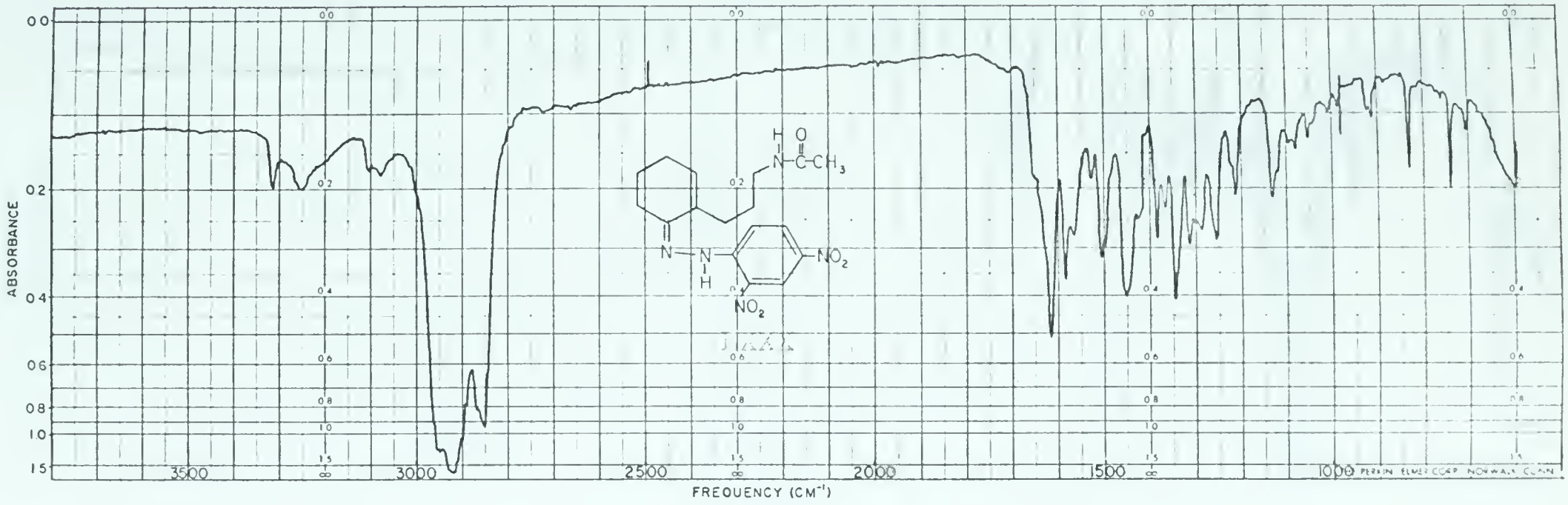


Figure 1

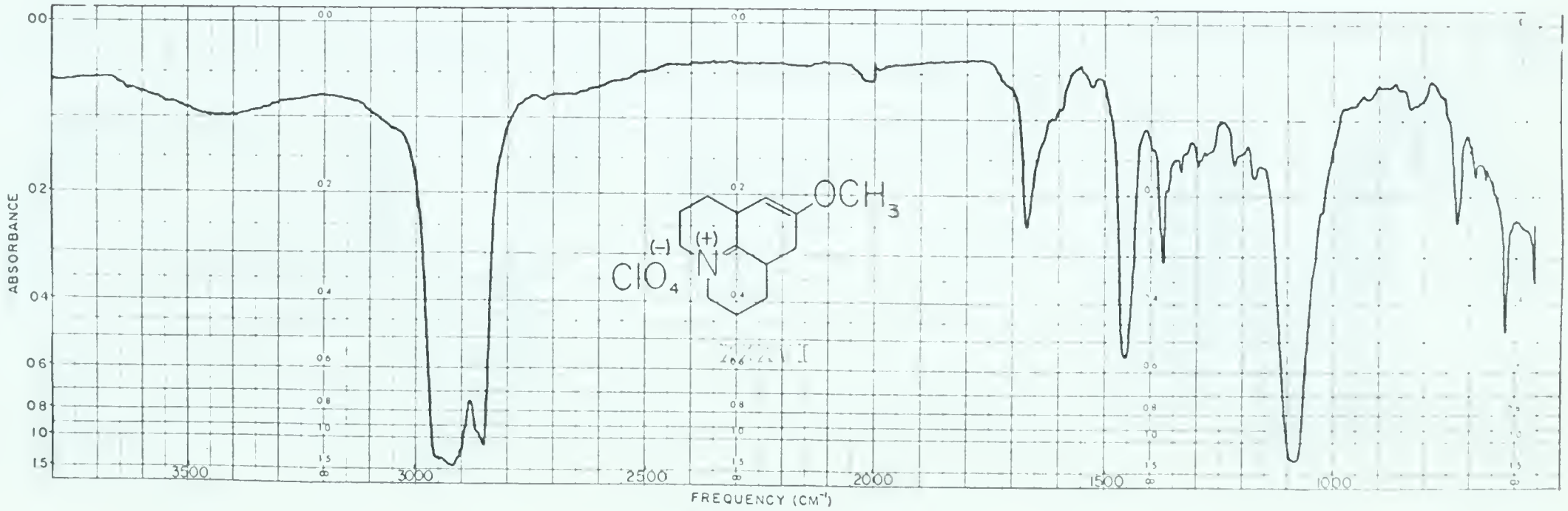
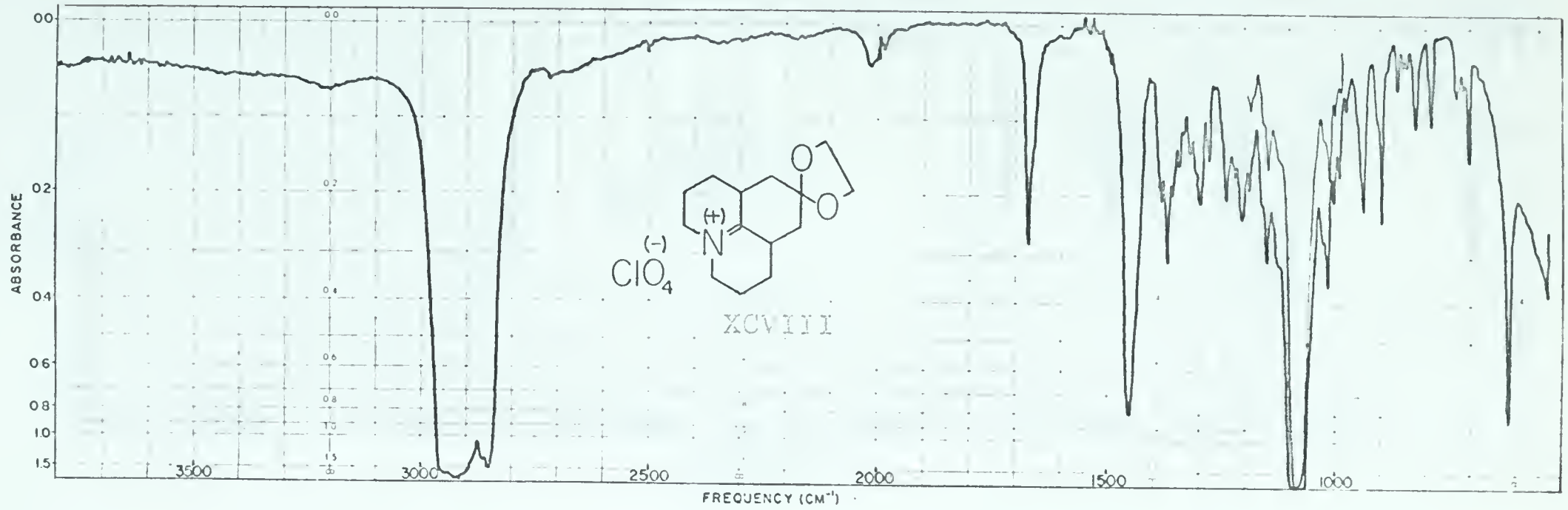
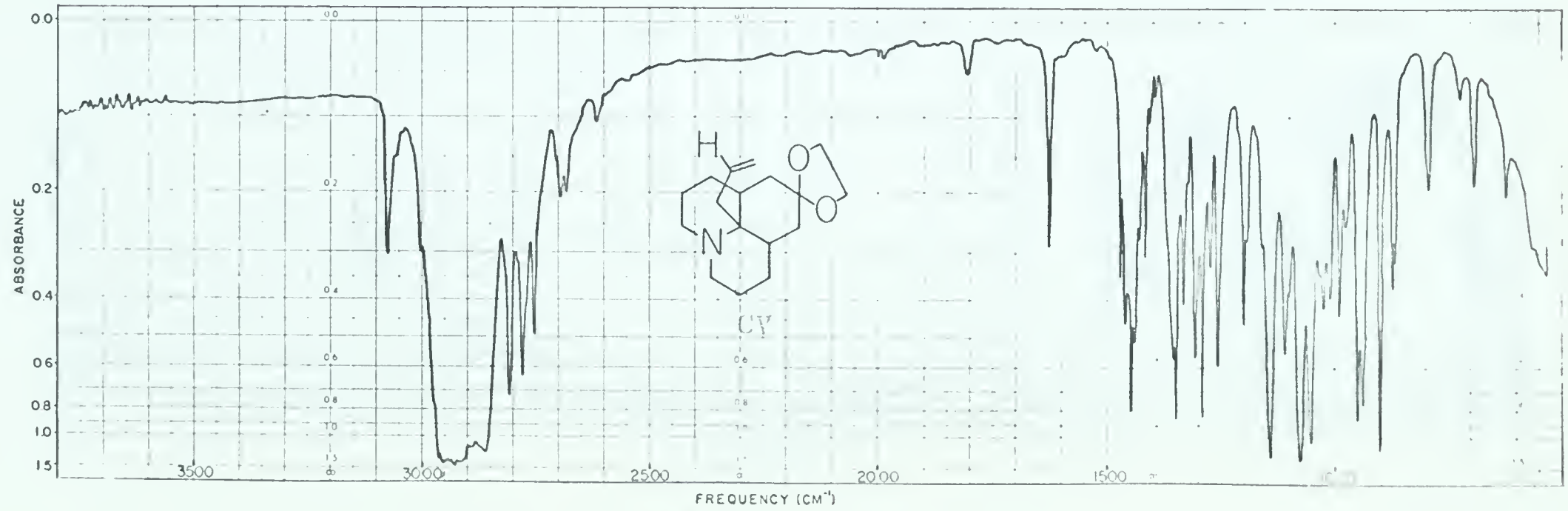


Figure 2



XCVIII

Figure 3



CV

Figure 4

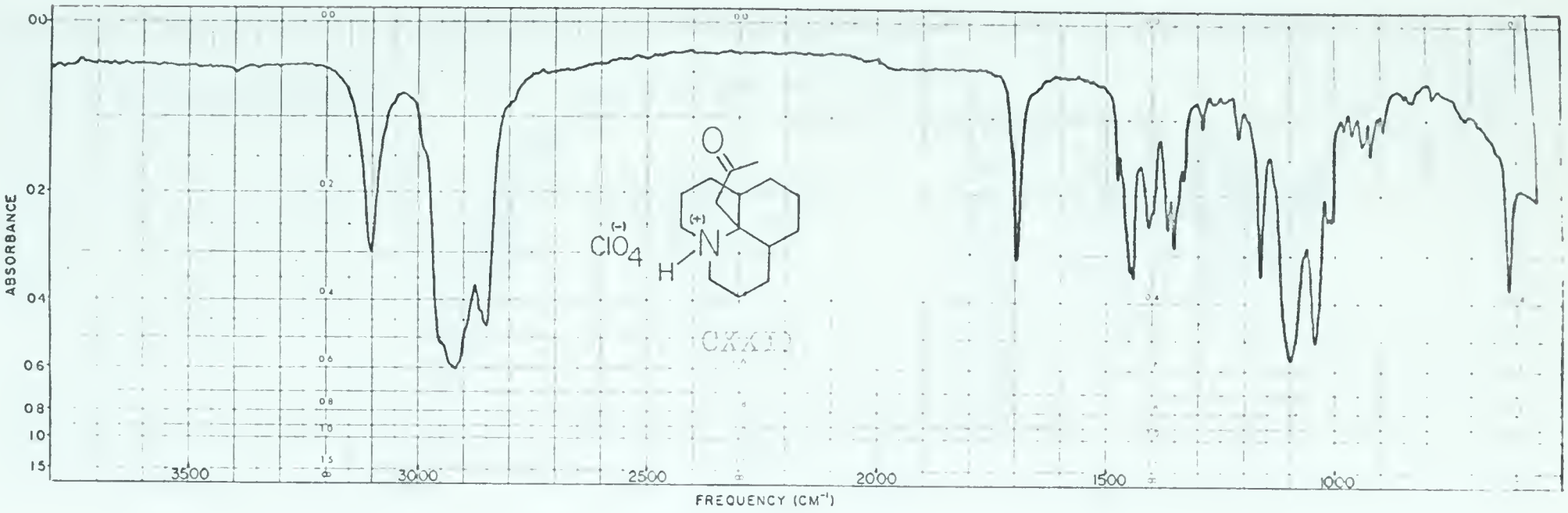


Figure 5

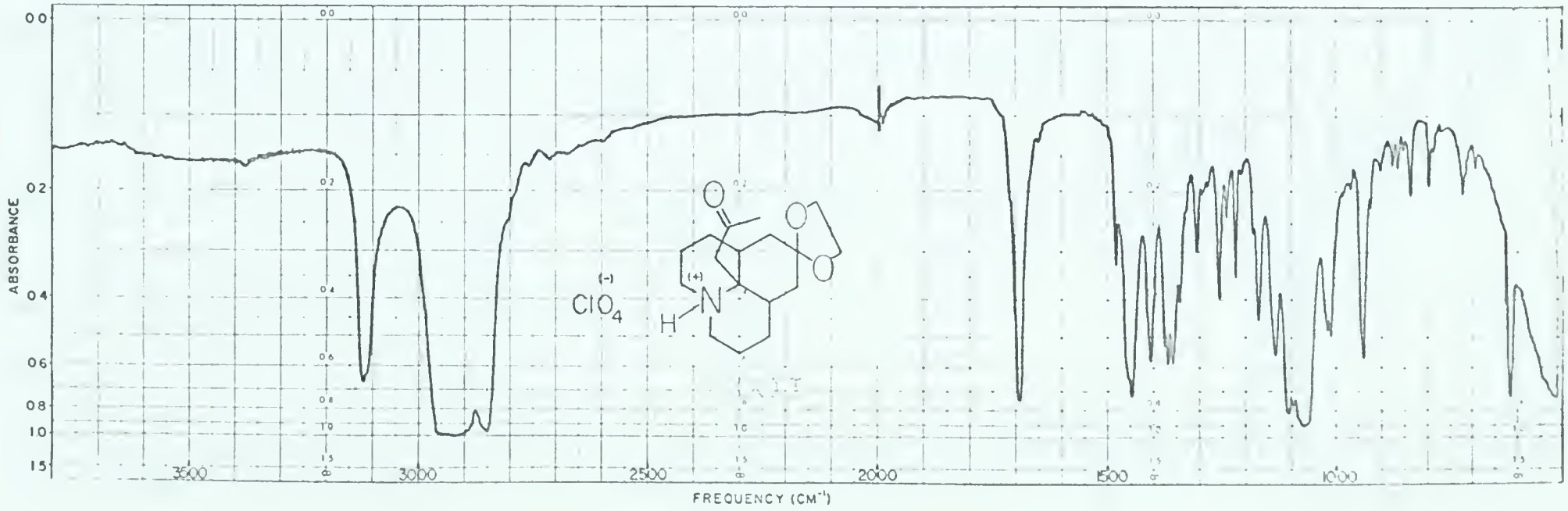
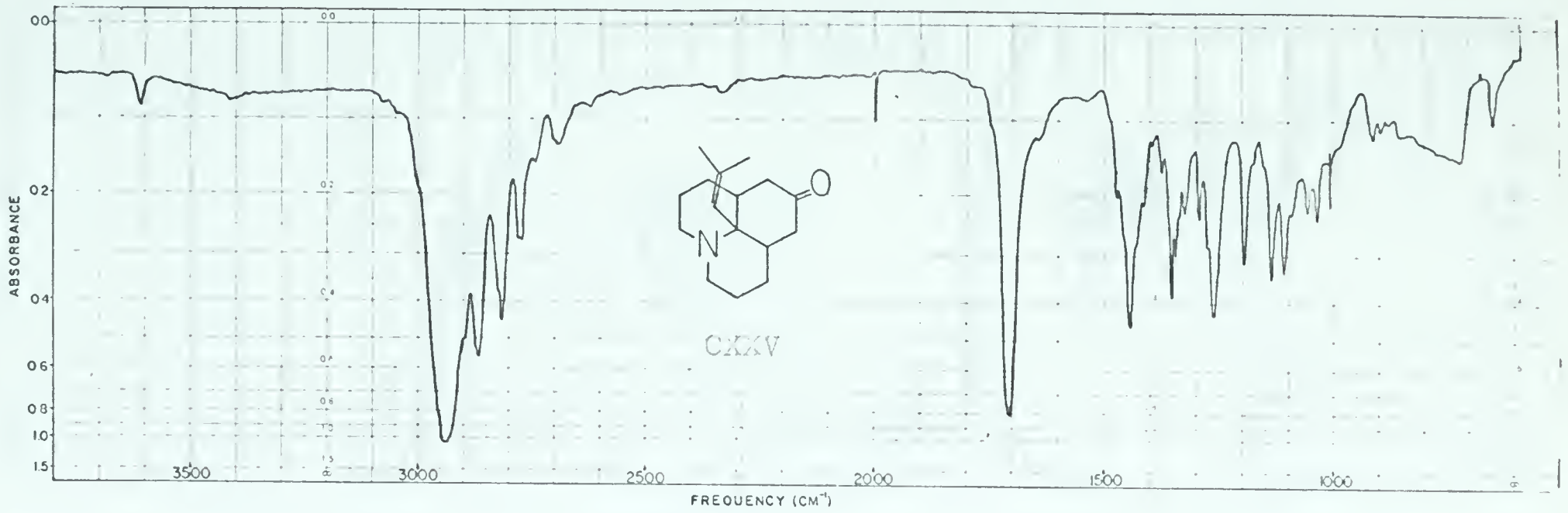


Figure 6



CXXV

Figure 7

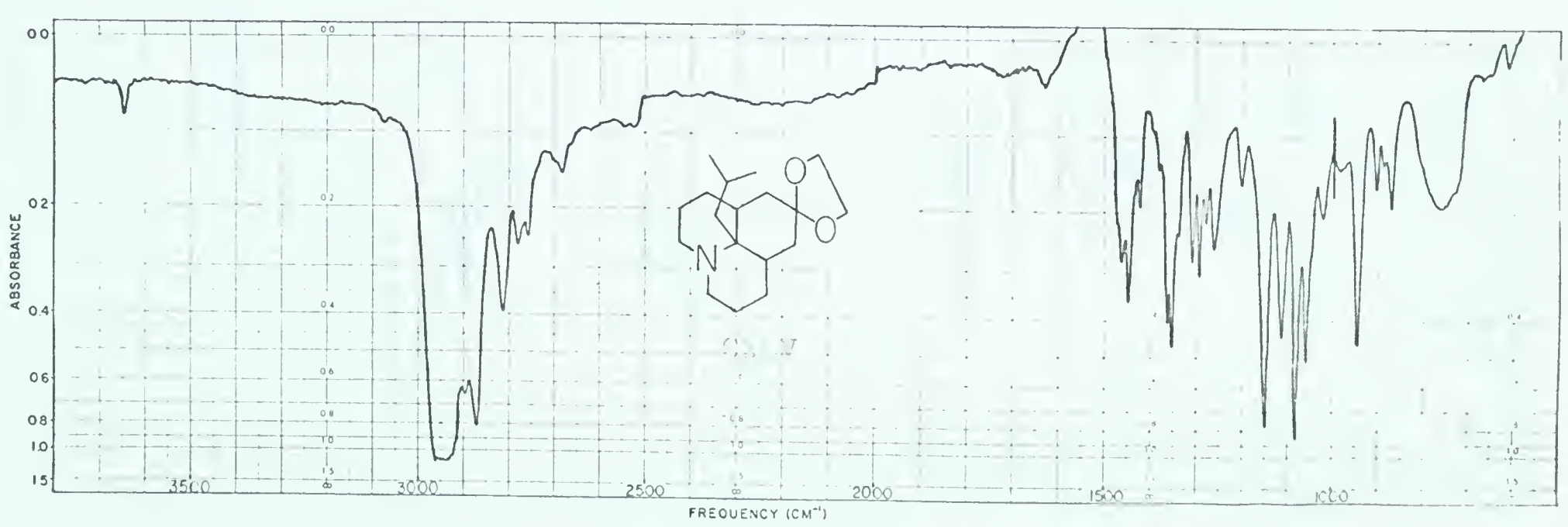


Figure 8

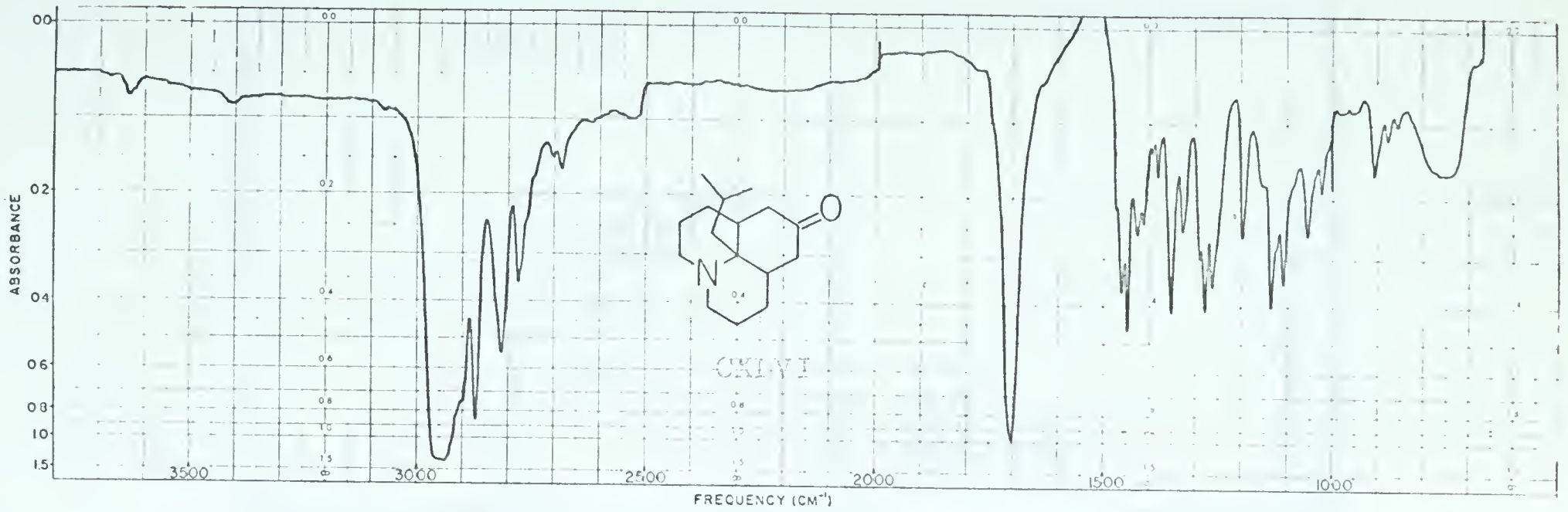


Figure 9

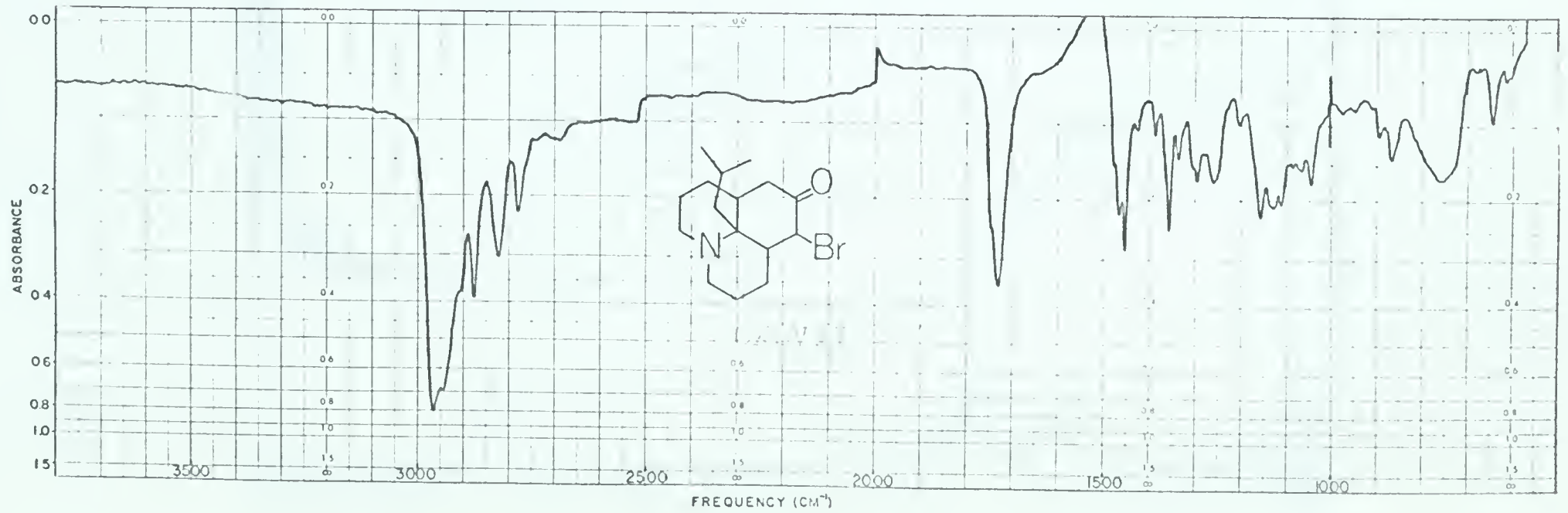
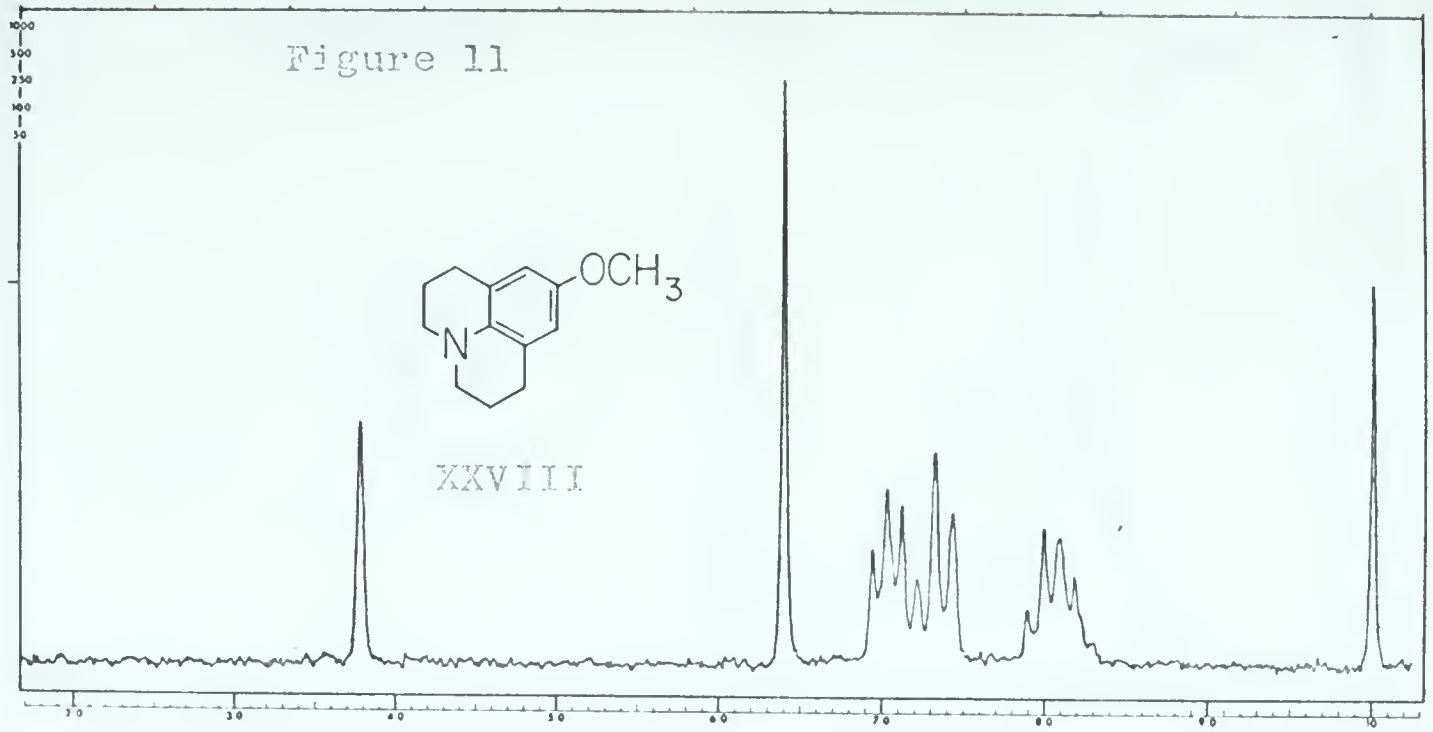


Figure 10

Figure 11



XXVIII

Figure 12

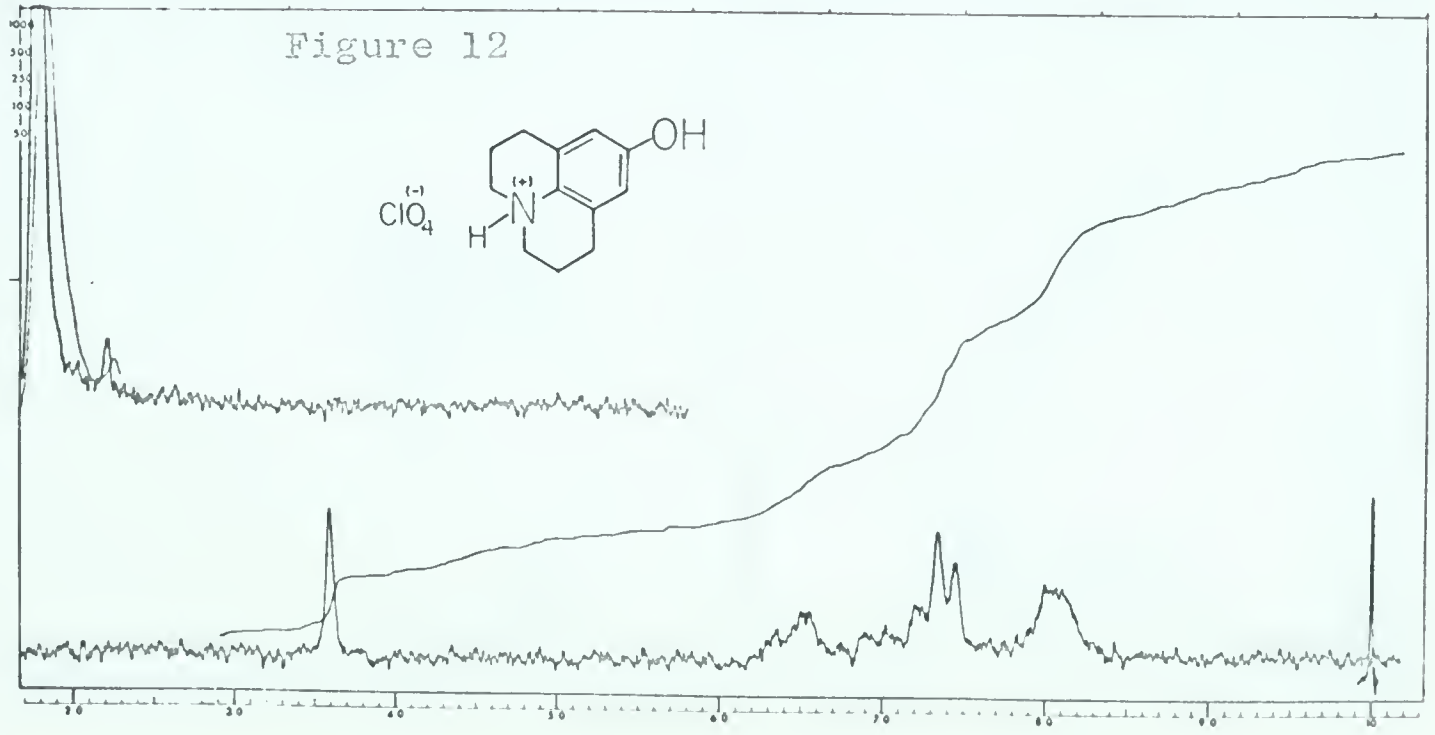
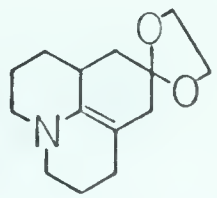
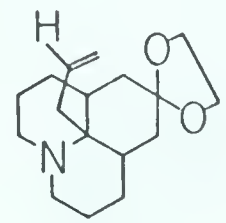


Figure 13



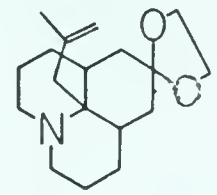
XCIX

Figure 14



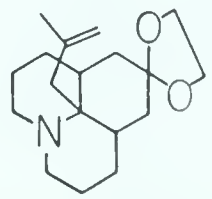
CV

Figure 15



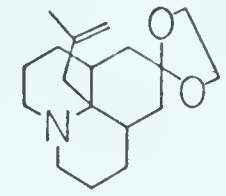
CVIII (CCl_4)

Figure 16



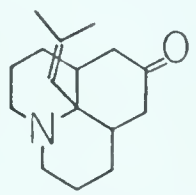
CVIII (benzene)

Figure 17



CXI (benzene)

Figure 18



CXXXV



FIGURE 19

FIGURE 20

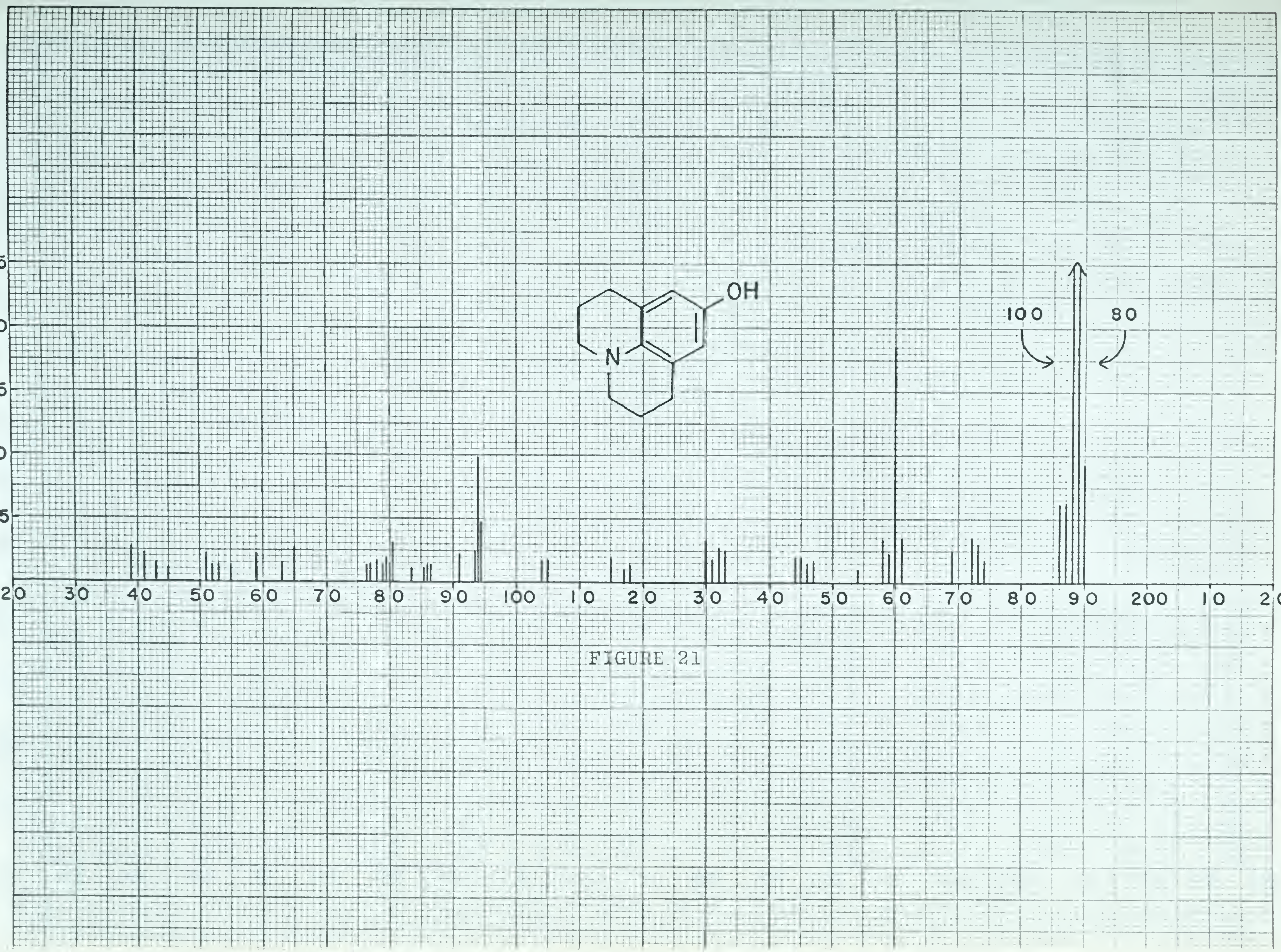
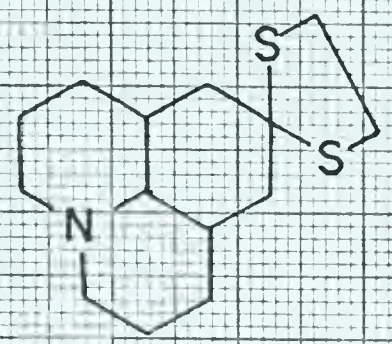

OH
N
100
80
25
20
15
10
5
20 30 40 50 60 70 80 90 100 10 20 30 40 50 60 70 80 90 200 10 20

FIGURE 21


S
S
N

100
60
55
50
45
40
35
30
25
20
15
10
5
75
85
95
105
115
125
135
145
155
165
175
185
195
205
215
225
235
245
255
265
275

FIGURE 22

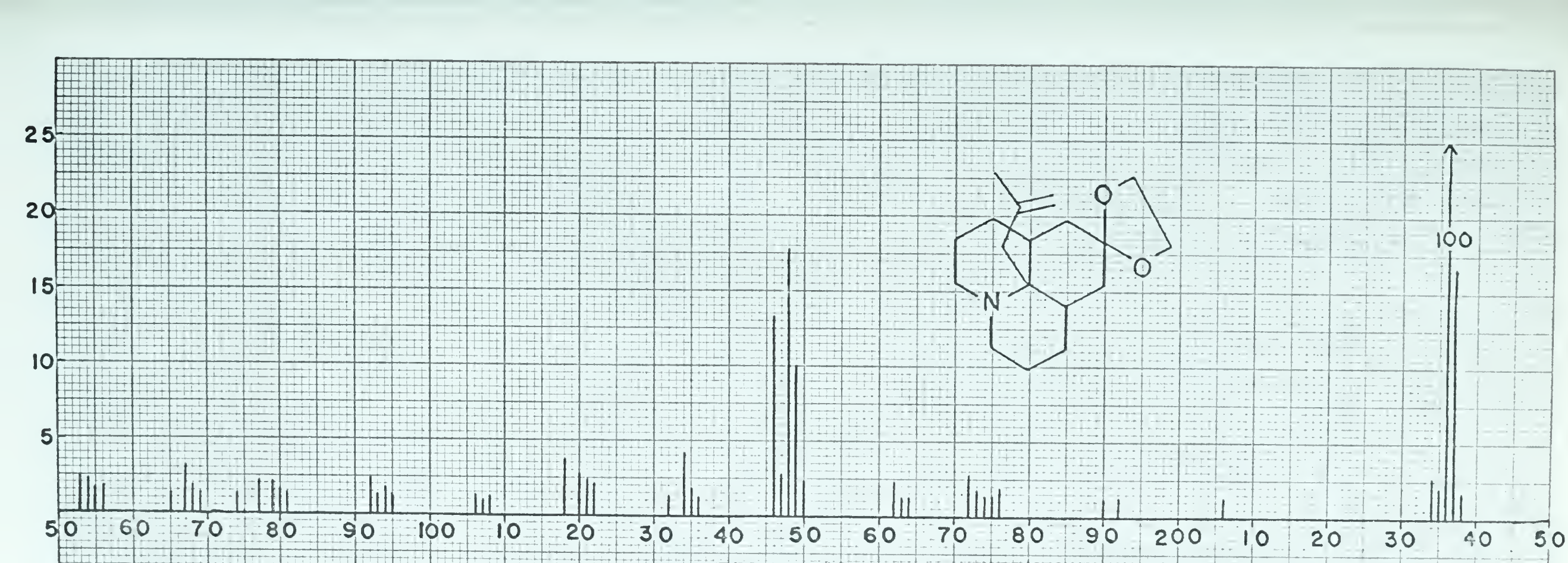


FIGURE 23

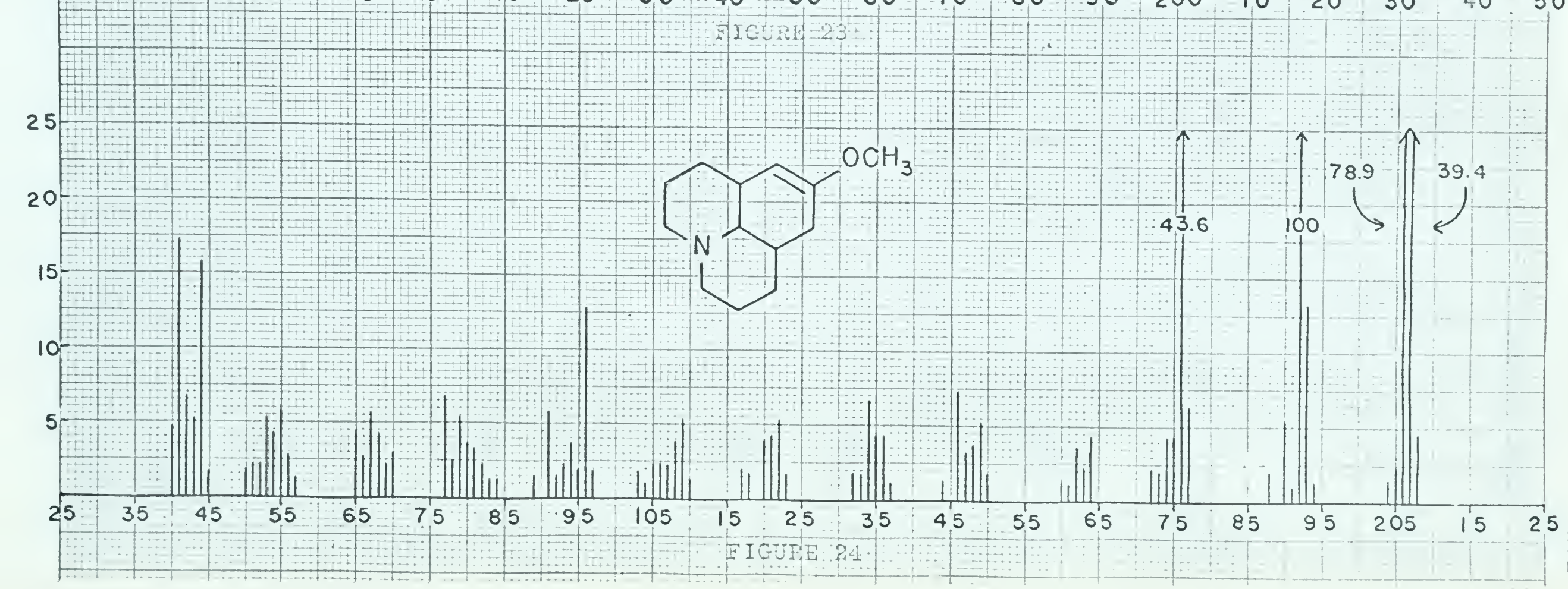


FIGURE 24

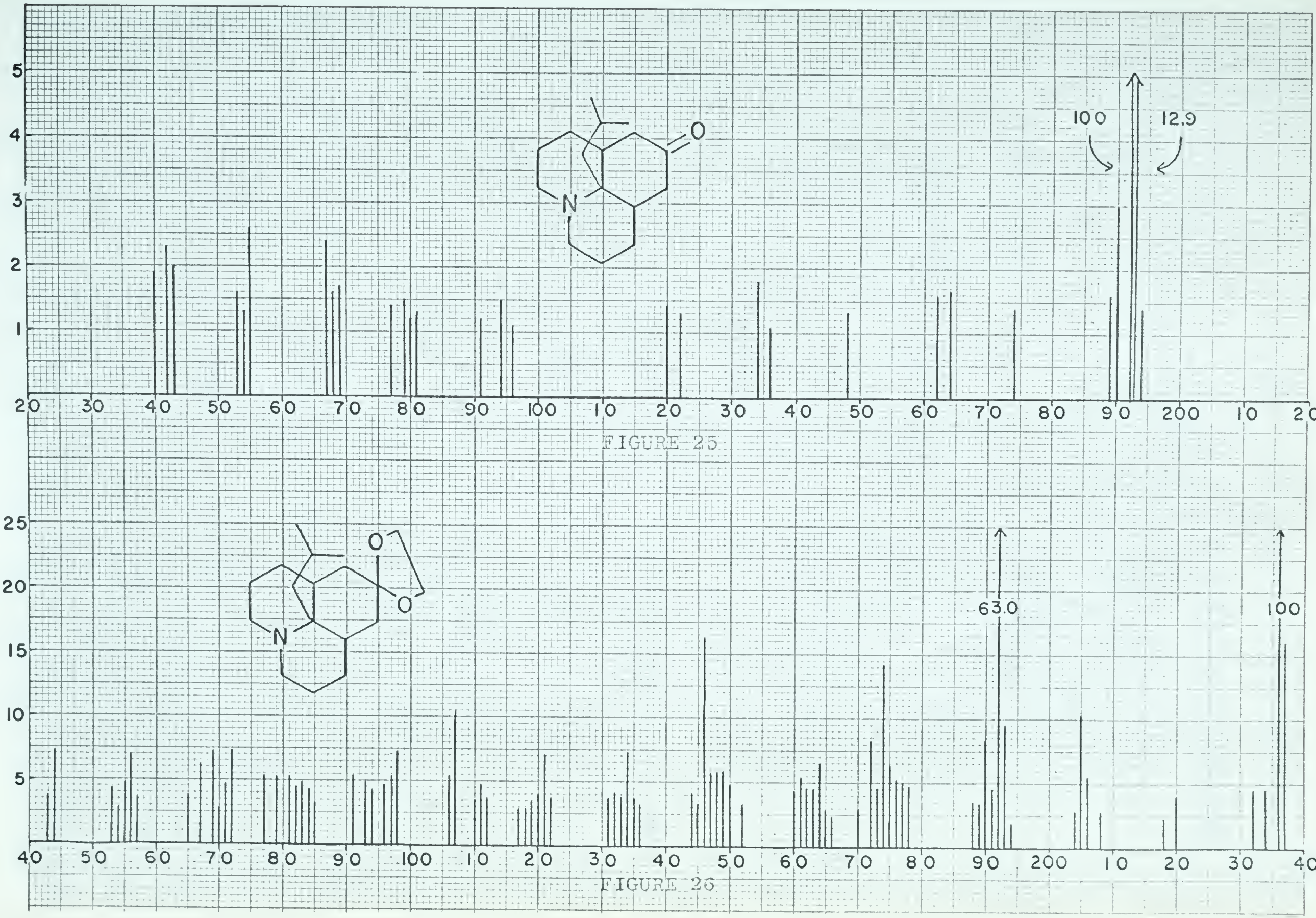


FIGURE 25

FIGURE 26

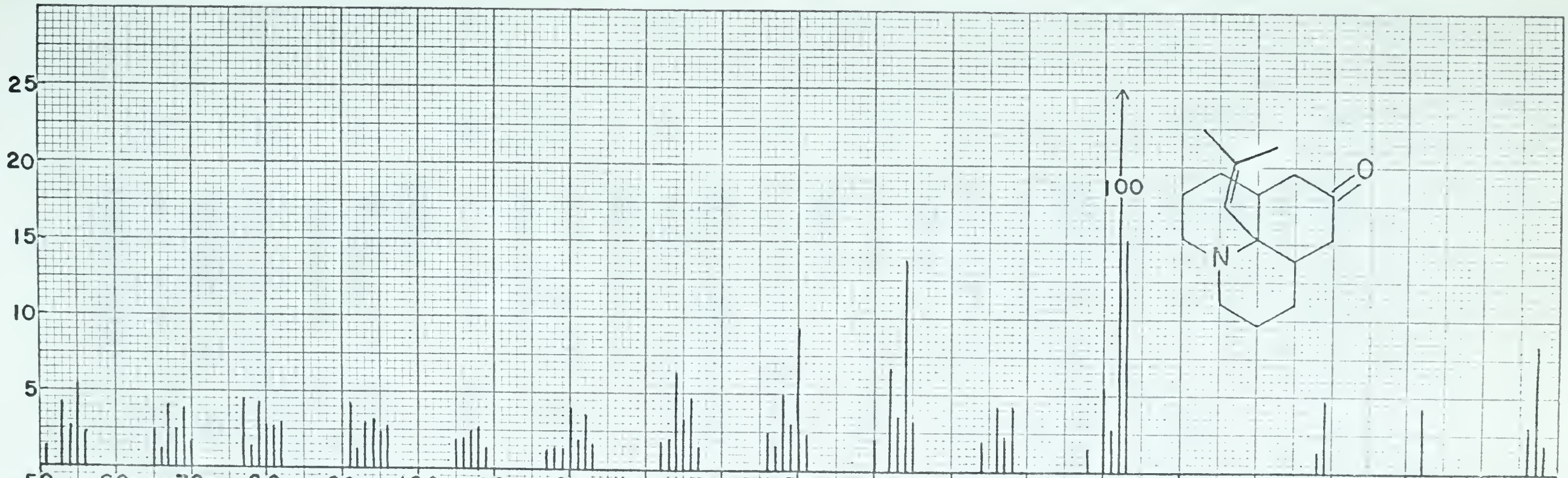


FIGURE 27

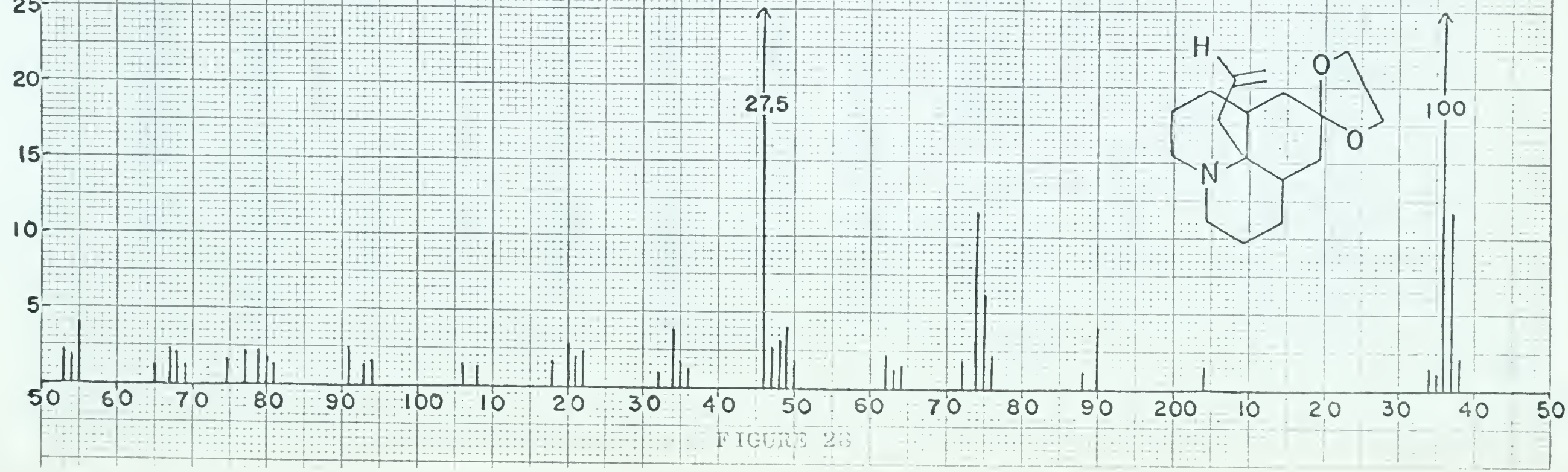


FIGURE 28

REFERENCES

1. Harrison W. A., Curcumelli-Rodostamo M., Carson D. F., Barclay L. R. C., MacLean D. B., Can. J. Chem. 39, 2086 (1961).
2. Anet F. A. L., Tet. Let., 20, 13 (1960).
3. Wiesner K., Ayer W. A., Fowler L. R., Valenta Z., Chemistry and Industry 564 (1957).
4. Przybylska M., Marion L., Can. J. Chem. 35, 409 (1957).
5. Przybylska M., Ahmed F. R., Acta Cryst., 11, 718 (1958).
6. Wiesner K., Valenta Z., et al., Tet. Let. 5, 187 (1961).
7. Ayer W. A., Berezowsky J. A. (Miss), Law D. A., Can. J. Chem. 41, 649 (1963).
8. French W. N., MacLean D. B., Chemistry and Industry 658 (1960).
9. Anet F. A. L., Khan N. H., Chemistry and Industry, 1238 (1960).
10. Ayer W. A., Iverach G. G., Can. J. Chem., 42, 2514 (1964).
11. Valenta Z., Yoshimura H., Rogers E. F., Ternbah M., Wiesner K., Tet. Let. 10, 26 (1960).
12. Ayer W. A., Berezowsky J. A. (Miss), Iverach G. G., Tet. Let. 18, 567 (1962).
13. Ayer W. A., Iverach G. G., Can. J. Chem. 38, 1823 (1960).

14. Anet F. A. L., Haq M. Z., Khan N. H., Ayer W. A., Hayatsu R., Valverde-Lopez S., Deslongchamps P., Riess W., Ternbah M., Valenta Z., Wiesner K., Tet. Let. 14, 751 (1964).

15. Ayer W. A., Jenkins J. K., Valverde-Lopez S., Tet. Let. 32, 2201 (1964).

16. Anet F. A. L., Rao M. V., Tet. Let., 20, 9 (1960).

17. Ayer W. A., Law D. A., Piers K., Tet. Let. 40, 2959 (1964).

18. Valenta Z., Deslongchamps P., Ellison R. A., Wiesner K., J. Am. Chem. Soc. 86, 2533 (1964).

19. Van Tamelen E. E., Foltz R. L., J. Am. Chem. Soc. 82, 502 (1960).

20. Birch A. J., J. Chem. Soc. 593 (1946).

21. Stork G., White W. N., J. Am. Chem. Soc. 78, 4604 (1956).

22. Dryden H. L., Webber G. M., Burtner R. R., Cella J. A., J. Org. Chem. 26, 3237 (1961).

23. Djerassi C., Editor, Steroid Reactions, Holden-Day, San Francisco, 1963, p. 267 et seq.

24. Leonard N. J., Steinhardt C. K., Lee C., J. Org. Chem. 27, 4027 (1962).

25. Bohlmann F., Chem. Ber. 91, 2157 (1958).

26. Tsuda K., Hayatsu R., J. Am. Chem. Soc. 77, 3089 (1955).

27. Nakazaki M., Isoe S., Bull. Chem. Soc. (Japan) 32, 1202 (1959).

28. Masamune S., J. Am. Chem. Soc. 86, 290 (1964).

29. Simons J. P., Quart. Revs. (London) 13, 3 (1959).

30. Nes W. R., Kostic R. B., Mosettig E., J. Am. Chem. Soc. 78, 436 (1956).

31. Westoo G., Acta. Chem. Scand. 7, 355 (1953); C. A. 48, 3349 (1954).

32. Rabe P., Ber. 37, 1671 (1904).

33. Farmer E. H., Ross J., J. Chem. Soc., 127, 2358 (1925).

34. Nightingale D. V., Erickson F. B., Shackelford J. M., J. Org. Chem. 17, 1005 (1952).

35. Cronyn M. W., Reisser G. H., J. Am. Chem. Soc., 75, 1664 (1953).

36. Cheronis N. D., Entrikin J. B., Semimicro Qualitative Organic Analysis, Interscience, New York, 1957, p. 223, Procedure B.

37. Spectrum kindly determined by J. B. Stothers, Department of Chemistry, University of Western Ontario, London, Ontario.

38. Nakanishi K., Practical Infrared Absorption Spectroscopy, Holden-Day, San Francisco, 1962, p. 223.

39. Tiers G. van D., Characteristic Nuclear Magnetic Resonance (NMR) "Shielding Values" (Spectral Positions) For Hydrogen in Organic Structures, Minnesota Mining and Manufacturing Company, St. Paul, 1958.

40. Stork G., Terrell R., Szmuszkovicz J., J. Am. Chem. Soc., 76, 2029 (1954).

41. Cohen L. A., Witkop B., J. Am. Chem. Soc., 77, 6595 (1955).

42. Adams W. J. (Mrs.), Kirk D. N., Patel D. K., Petrow V., Stuart-Webb I. A. (Mrs.), J. Chem. Soc. 2298 (1954).

43. Corey E. J., Topie T. H., Wozniak W. A., J. Am. Chem. Soc. 77, 5415 (1955).

44. Jones R. N., Ramsay D. A., Herling F., Dobriner K., J. Chem. Soc. 2898 (1952).

45. Warnhoff E. W., Johnson W. S., J. Am. Chem. Soc., 75, 494 (1953) and references cited therein.

46. Wallach O., Ann. 359, 303 (1908).

47. Gillam A. E., Stern E. S., An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry, Edward Arnold, London, 1954.

48. Jackman L. M., Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, 1959, p. 103.

49. Phillips W. D., J. Chem. Phys., 23, 1363 (1955).

50. Fraenkel G., Loewenstein A., Meiboom S., J. Phys. Chem. 65, 700 (1961), and earlier references cited therein.

51. Patterson A. M., Capell L. T., Walker D. F., The Ring Index, American Chemical Society, Washington, 1960, 2nd Edition, p.452, Ring 3493.

52. Pratesi P., Castoring G., Il Pharmaco (Pavia) Ed. Sci, 9, 205 (1954). C. A. 6258g (1955).

53. Organic Syntheses, John Wiley, New York, 1944, Vol. 26, p. 40.

54. Beilsteins Handbuch der Organischen Chemie, Edwards Brothers, Ann Arbour, 1944, 5th Edition, Vol. XXI, p. 61.

55. Leonard N. J., J. Am. Chem. Soc. 78, 1984 (1956).

56. Kalvoda J., Anner G., Arigoni D., Heusler K., Immer H., Jeger O., Mihailovic M. Lj., Schaffner K., Wettstein A., Helv. Chim. Acta 44, 186 (1961).

57. Soper J. A. C., private communication.

58. Bohlmann F., Arndt C., Angew. Chem. 91, 2167 (1958).

59. Horner L., Schaefer H., Ludwig W., Chem. Ber. 91, 75 (1958).

60. Stork G., Darling S. D., J. Am. Chem. Soc. 86, 1761 (1964).

61. MacLean D. B., Can. J. Chem. 41, 2654 (1963).

62. Law D. A., Ph.D. Thesis, University of Alberta, 1963.

63. Spiteller G., Spiteller-Friedman M., Monatsh. 93, 1395 (1962).

64. Micovic V. M., Mihailovic M. L., J. Org. Chem. 18, 1198 (1953).

65. Bobbit J. M., Thin Layer Chromatography, Reinhold, New York, 1963, p. 93.

66. Fieser L. F., Experiments in Organic Chemistry, Heath, Boston, 1957, p. 299.

B29832